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PROSTAGLANDINS, LEUKOTRIENES, AND PLATELET-ACTIVATING FACTOR IN SHOCK[1]

Giora Feuerstein and John M. Hallenbeck

Neurobiology Research Division, Department of Neurology, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, Maryland 20814-4799

INTRODUCTION

Shock is commonly defined as acute circulatory collapse due to dramatic decrease in blood volume, failure of cardiac or vascular circulation or of neurogenic control of the circulation. In essence, shock is inadequate tissue perfusion that impairs normal organ functions. As such, shock may be reversible (i.e. correction of the impaired organ perfusion leads to restoration of organ functions) or nonreversible (where noncorrectable damage was already produced during the low blood flow state). Irreversible shock leads to organ death and, if essential organs are involved, to death of the animal.

This review compiles the available evidence on the potential role of several vasoactive lipids in the pathophysiology of shock and provides an analysis of the potential interactions of these vasoactive lipids during various shock paradigms. We emphasize the role of the more recently discovered vasoactive lipids, leukotrienes (LTs), and platelet-activating factor (PAF) in shock and trauma and refer briefly to prostaglandins (PGs) and thromboxane A_2 (TXA_2), which have been extensively studied and reviewed in the past decade (1, 2).

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PROSTAGLANDIN (PG) E_2, D_2, $F_{2\alpha}$ AND PGI_2 IN SHOCK

Numerous studies conducted in a variety of shock models show that circulating levels of the classical prostaglandins (e.g. PGE_2, $PGF_{2\alpha}$) are elevated in several shock states (1–3). Although bioassy techniques were used for much of the original work, confirmation has largely been obtained using radioimmunoassay procedures (1). Recent studies also demonstrate high levels of 6-keto-$PGF_{1\alpha}$ (a stable metabolite of PGI_2; Figure 1) in the circulation of animals subjected to various shock situations, including endotoxic (1, 4, 5), hemorrhagic (6), mycotoxic (7), and traumatic (8). Elevated levels of 6-keto-$PGF_{1\alpha}$ also occur in patients with septic shock (9). However, the significance of PG production in the various shock models is still unknown.

The recuperation of hemodynamic, endocrine, and metabolic functions was enhanced in endotoxic, traumatic, or hemorrhagic shock in which PGEs or PGI_2 was administered before or after the shock (1, 10–13). Furthermore, survival of dogs treated with PGD_2 during endotoxemia (14) was increased, as was survival of rats exposed to hemorrhage and treated with PGI_2 (12) or 16,16-dimethyl PGE_1 (10). However, the protective capacity of the vasodilator PGs (PGEs, PGI_2) across species and shock paradigms is controversial (1).

While selected prostanoids (primarily PGEs, PGI_2) are beneficial in several shock models, inhibition of eicosanoid production also provides protection in

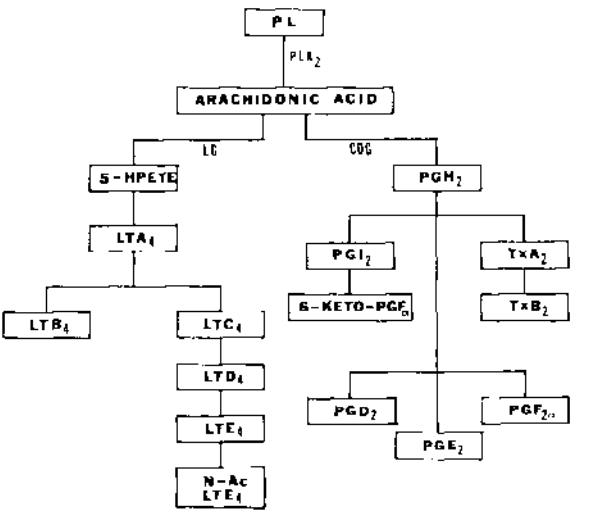

Figure 1 The cascade of arachidonate metabolism. Abbreviations: COG, cyclooxygenase pathway; LG, 5-lipoxygenase pathway; PLA_2, phospholipase A_2; PL, phospholipids.

various shock models. This phenomenon was first described by Northover & Subramanian. These investigators used acetyl-salicylic acid in endotoxic shock (15), and this inhibition was confirmed with several other nonsteroidal antiinflammatory drugs (NSAID) (1, 2). However, the beneficial effects of drugs that inhibit prostanoid synthesis occur primarily in endotoxic shock; in hemorrhagic shock, limited information indicates that inhibition of eicosanoid production exacerbates the hemodynamic derangements and decreases the incidence of survival from acute hypovolemic hypotension (6, 16, 17). Furthermore, some investigators have raised doubts about the detrimental role of eicosanoids even in endotoxic shock. Effective blockade of eicosanoid production by BW 755c (a dual lipoxygenase and cyclooxygenase inhibitor) in endotoxemia failed to improve survival or reduce detrimental outcomes of the endotoxin (5). Thus, although earlier views favored a pathological role for prostanoids in endotoxemia and the use of drugs that inhibit PG synthesis to improve survival in such syndromes (2), it is still unclear whether the beneficial actions demonstrated by NSAID are actually due to inhibition of eicosanoid production or, instead, to other pharmacologic properties of such agents.

THROMBOXANE A_2 IN SHOCK AND TRAUMA

Thromboxane A_2 (TXA_2) is one of the most potent arachidonic acid (AA) metabolites. It is produced by the cyclooxygenase and TXA_2-synthetase enzyme complexes (Figure 1). TXA_2 has an extremely short half-life (~30 sec) under normal biological conditions (pH = 7.4; 37°C); therefore, TXB_2, a stable and virtually nonactive metabolite of TXA_2 (Figure 1), is used to monitor levels of TXA_2. Several lines of evidence support a role for TXA_2 as a mediator of shock. Elevated plasma and lymph levels of TXB_2 are consistently found in a variety of experimental shock models, such as endotoxemic (18), traumatic (19), or hemorrhagic (6). Moreover, increased plasma levels of TXB_2 in humans suffering from severe septic shock were also reported (20).

Two major pathophysiological processes can be attributed to TXA_2. First, TXA_2 is a potent vasoconstrictor of small and large blood vessels; second, TXA_2 is an extremely potent platelet-aggregating factor. These effects have been demonstrated across all species (for review see 21). These two primary actions of TXA_2 are believed to act together to interfere with organ blood flow and promote ischemia in several shock states. Excessive TXA_2 production is considered to play a primary role in massive pulmonary thrombosis following AA or heterologous blood administration in various species (21, 22).

The role of TXA_2 and its endoperoxide precursor (PGH_2; Figure 1) in the pathophysiology of various shock states is also suggested by experiments

demonstrating the therapeutic value of TXA_2 antagonists or synthesis inhibitors in such situations. Thus, the TXA_2 receptor antagonist EP 092 blocks the development of pulmonary hypertension in endotoxemia (23), and structurally different TXA_2 antagonists such as pinane-TXA_2 have a similar protective effect (24). However, all the TXA_2 antagonists are also PGH_2 antagonists. Therefore, it is not yet possible to evaluate the relative roles of PGH_2 and TXA_2 in shock. Furthermore, TXA_2 synthesis inhibitors have therapeutic efficacy in several shock and trauma models. UK 37248 and other TXA_2-synthetase inhibitors are effective in rat endotoxic shock (25, 26) and arachidonate-induced sudden death in rabbits (27), and U 63,557A has a protective effect in rat trauma (19). However, TXA_2 inhibition fails to modify the outcome of gram-negative septic shock (28).

Interestingly, TXA_2 synthesis inhibitors might not act only by inhibiting TXA_2 synthesis. They might also increase the availability of endoperoxides for the PGI_2 synthetase pathway by producing more PGI_2 (29).

LEUKOTRIENES IN SHOCK AND TRAUMA

Production of leukotrienes (LTs; Figure 1) in acute anaphylaxis is considered to play a major role in the cardiorespiratory derangements that lead to shock and death (30-33). The role of LTs in other forms of shock such as sepsis, trauma, or hemorrhage is still unclear, primarily owing to difficulties in assaying leukotrienes in biological tissues and fluids. Some recent evidence supports the generation of LTs in nonimmune pathophysiological processes (e.g. burns, trauma) by following the levels of LTs in the bile. Large increments of LTE_4 and *N*-acetyl-LTE_4 (Figure 1) are found in the plasma and bile of rats exposed to various traumatic injuries such as burns, bone fracture, abdominal surgery (34), and endotoxemia (35). This new evidence confirms earlier suggestions that were based on increases in 5-HETE derivative of 5-HPETE (Figure 1) in the lymph during endotoxemia (36) and the enhanced release of LTC_4 from mouse peritoneal macrophages exposed to endotoxin in vitro (37).

Although LTs have been argued to be rapidly cleared from the blood, metabolized by the liver, and excreted in the bile as nonactive metabolites, recent experiments indicate LTs have an enterohepatic cycle (38). In species where *N*-acetyl-LTE_4 is the major LT metabolite to reenter the circulation from the gut, little biological action can be anticipated since *N*-acetyl-LTE_4, is less than 1% as effective as LTE_4 (39). However, in species where LTE_4 is the major metabolite to reenter the circulation (e.g. the cynomolgus monkey) substantial potentiation and prolongation of the LT effects can be anticipated, since LTE_4 duplicates many of the biological activities of LTC_4/LTD_4 (40).

Numerous articles have described the effects of LTs on the various com-

ponents of the cardiorespiratory system, blood vessels, and the microcirculation (31–34). The key pathophysiological consequences include: (*a*) reduction in cardiac output; (*b*) constriction of blood vessels and reduction in organ blood flow (31, 32) [exceptions to (*b*) are the rabbit cerebral arterioles (41), the canine renal and mesenteric arteries in vitro (42), and the differential vascular responses to LTs that may occur in various segments of blood vessels (43)]; (*c*) bronchoconstriction, reduced lung compliance, and increases in pulmonary vascular resistance (31, 32); (*d*) increases in postcapillary venular permeability and venoconstriction that lead to pronounced plasma extravasation and reduction in blood volume (31, 32, 44); and (*e*) aggregation and activation of platelets and white blood cells contributing to circulatory shock. Formation of microthrombi in the lung and release of multiple secondary mediators from activated white blood cells and macrophages such as TXA_2, PGs, kinins, oxygen radicals, and histamine amplify and confound the direct effects of the LTs. The multiple sites of LT actions on the cardiovascular system and the summation of these effects to produce shock are summarized in Figure 2.

A third line of evidence that supports the role of LTs in the pathophysiological events of shock and trauma is derived from experiments utilizing LT antagonists in treatment of various shock states. Two LT antagonists have been evaluated so far: (*a*) FPL-55712, a short-acting LTC_4/D_4 antagonist, protects mice from lethal endotoxemia (45) and (*b*) LY 171,883, a longer and more potent LTD_4/E_4 antagonist, also provides some protection against endotoxemia (46) and traumatic shock (47) in rats. Furthermore, several inhibitors of the lipoxygenase pathway of arachidonate metabolism (e.g. CGS-5391B, U-60,257, diethylcarbamazine, propylgallate) have protective effects in traumatic and endotoxic shock (21). However, these data must be interpreted with caution, since none of the available lipoxygenase inhibitors is highly specific for the 5-lipoxygenase enzyme complex; at high concentrations these compounds also inhibit the cyclooxygenase pathway (48). Interestingly, the tripeptide thyrotropin-releasing hormone (TRH) also reverses the hypotension produced by LTD_4 in several species through a central mechanism of action (49). More potent and specific LT antagonists and synthesis inhibitors with clearly delineated actions are necessary to further elucidate the role of LTs in selective pathophysiological processes.

PLATELET-ACTIVATING FACTOR IN SHOCK AND TRAUMA

The term *platelet-activating factor* (PAF) proposed by Benveniste et al (50) originally defined the most prominent biological activity of a new class of phospholipids released from basophils by immune (IgE) stimuli. The chemi-

cal nature of these phospholipids is 1-O-alkyl-2-acetyl-*sn*-glycero-3-phosphorylcholine (51, 52). This novel group of compounds has diverse biological action and is released from a variety of cell types, e.g. polymorphonuclear and endothelial cells and by immune and nonimmune stimuli (53, 54).

Understanding of the role of PAF in shock states was based on the demonstration that administration of PAF to several species (guinea pig, rat, rabbit, dog, pig) produced severe hypotension, shock, and death (56–59). In fact, PAF is the single most potent agent to cause shock when administered systemically (Figure 3). The shock syndrome produced by PAF involves

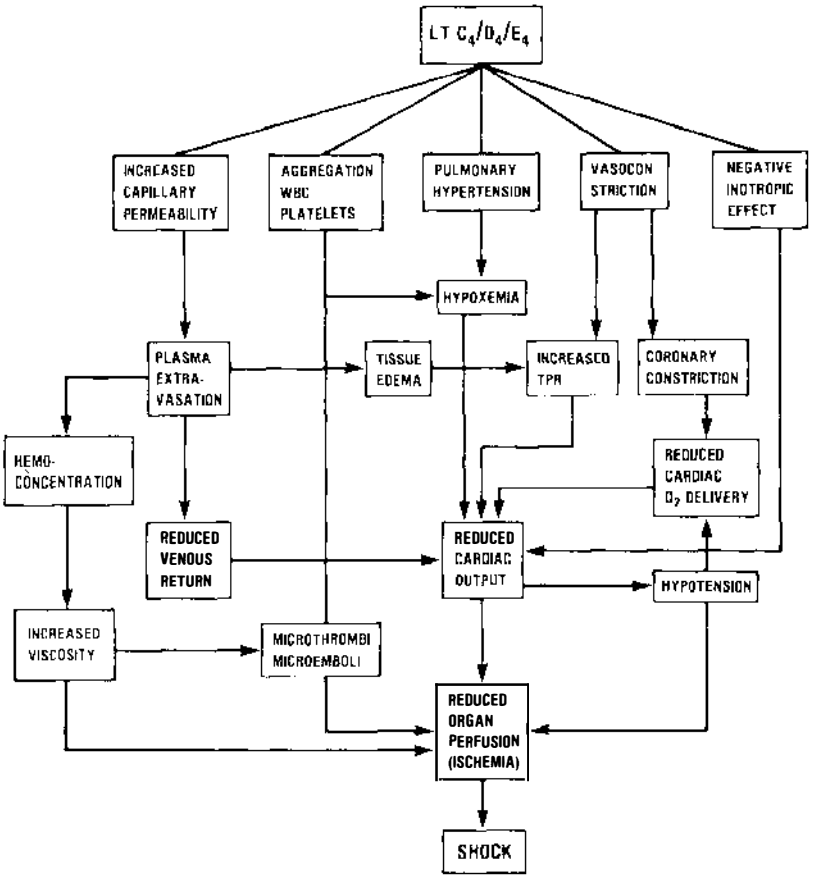

Figure 2 Schematic presentation of the cardiovascular effects of peptide leukotrienes, which lead to shock. TPR = total peripheral resistance. See text for detailed discussion of the multiple sites of the LT actions on the cardiovascular system.

several mechanisms and sites of action: First, pulmonary circulation is affected by an increase in pulmonary vascular resistance (PVR) (55, 59) and bronchoconstriction, both of which contribute to hypoxemia; the increase in PVR contributes to right heart failure (59). Also, the heart is affected by reduction in cardiac output due to coronary constriction (59–61), reduction in myocardial contractility (62–64), and reduced cardiac preload (58). However, some controversy exists as to whether PAF directly affects the myocardium (65) or whether reduction in O_2 leads to a secondary effect stemming from coronary vasoconstriction (60). Also, the PAF-induced coronary constriction and cardiac failure seem to be mediated, at least in part, by TXA_2, since much of the cardiac effect of PAF can be blocked by indomethacin (a potent inhibitor of prostaglandin synthesis) (60). Third, peripheral circulation is affected by vasodilation, which might also contribute to the hypotensive effect of PAF; the vasodilation produced by PAF is not mediated by eicosanoids (60, 61). Fourth, vascular permeability is altered. PAF increases vascular permeability and extravasates plasma to the tissue. This action ultimately results in contraction of blood and plasma volume, which contributes to the reduction in cardiac output (58). Finally, regarding activation of blood cells: activation and aggregation of white blood cells and platelets primarily in the pulmonary circulation contributes to elevation of PVR and reduces lung perfusion. Moreover, these activated blood cells release secondary mediators such as serotonin, TXA_2, leukotrienes, prostaglandins, vasoactive peptides, and oxygen radicals. These secondary mediators promote cell membrane damage, increase vascular permeability, and initiate proinflammatory processes. No other vasoactive lipid known to date produces sustained derangements in organ blood flow at doses as low as those shown in Figure 3.

Although many articles reported that PAF can cause circulatory collapse and death in several species, only a few reports documented the presence of PAF in organs or in the circulation during shock states. Elevated plasma levels of PAF were found in *E. coli* endotoxemia (66). Also, release of PAF from macrophages and spleen lymphocytes was enhanced in rats exposed to bacterial peritonitis (67).

Recent studies using selective and potent PAF antagonists provide additional support for the role of PAF in the pathophysiology of various shock syndromes. Such compounds (e.g. kadsurenone, CV 3988, BN 52021) have recently been described and examined in a variety of immune and nonimmune shock models. Kadsurenone reverses the lipopolysaccharide (LPS)-induced hypotension (66), whereas CV 3988 increases survival of rats exposed to LPS endotoxemia (68). BN 52021 reverses and prevents the effects of *Salmonella typhimurium* endotoxin (69, 70). Kadsurenone also provides additional protection in acute antigen anaphylaxis (71).

In summary, PAF can produce hypotension and shock through direct and

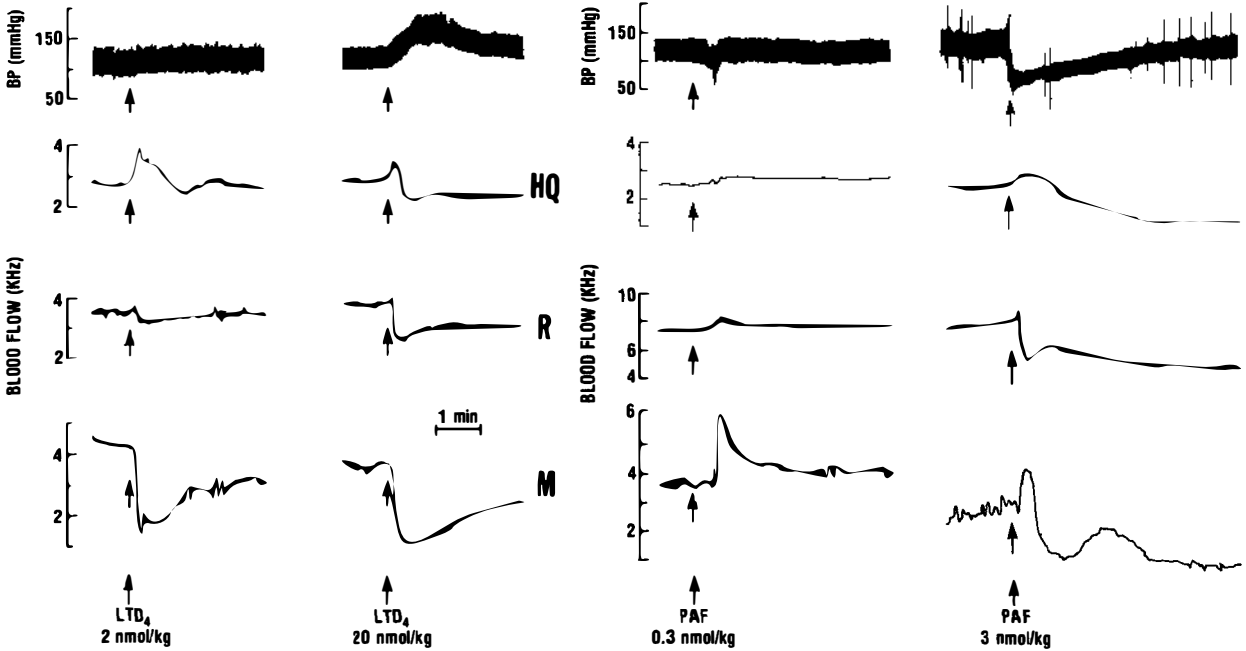

Figure 3 Comparison of LT and PAF effects on blood pressure and organ blood flow in the conscious rat. Abbreviations: HQ, hindquarters blood flow; R, renal blood flow; M, mesenteric blood flow. Time scale of 1 min is given in the figure. Vasodilator effect of PAF at low doses (0.3 nmol/kg) in the M is in marked contrast to the effect of LTD_4; a larger dose of PAF severely reduces HQ, R, and M blood flow in spite of recovery of the systemic blood pressure. Therefore, inadequate organ blood flow leads to shock while the systemic hemodynamic induces (e.g. BP) are still within a normal range.

indirect (e.g. TXA_2 of LT-mediated) actions on the heart, pulmonary system, blood vessels, and the microcirculation. Evidence supporting the role of PAF in shock states includes direct biochemical evidence as well as pharmacological studies using PAF antagonists. No specific PAF-acether synthesis inhibitor has been described to date.

SUMMARY AND CONCLUSION

Three major lines of evidence support a role of eicosanoids and PAF in shock. Formation of each of the cyclooxygenase metabolites of arachidonate is enhanced at some point during the shock; these metabolites include PGE_2, $PGF_{2\alpha}$, PGI_2, and TXA_2. Enhanced formation of 5-HETE and the cysteinyl-LTs provides evidence for activation of the 5-lipoxygenase pathway of arachidonate metabolism, and preliminary biochemical evidence suggests that formation of PAF in anaphylactic and endotoxic shock is also enhanced. Second, TXA_2, cysteinyl-leukotrienes, and, to an even greater extent, PAF are able to produce shock and death in intact animals. Third, pharmacological studies show that selective antagonists or synthesis inhibitors modify the course of the shock.

While any of these lines of evidence may not by itself provide proof for a cause–effect relationship, the data taken together strongly suggest that vasoactive lipids might be involved in fundamental processes in the pathophysiology of shock. However, the role of vasoactive lipids might vary in different shock paradigms, change at various time points during the evolution of the shock, and depend on the species studied. Moreover, while the majority of the reports tend to focus on a specific substance, the metabolism of all of the eicosanoids mentioned, as well as PAF and probably other arachidonate metabolites (e.g. 15-lipoxygenase products such as lipoxins), changes during shock states. This fact probably causes most of the discrepancies in studies using specific antagonists or synthesis inhibitors to modify the state of shock. Thus, while blockade of one mediator might provide some protection, it might not be sufficient to halt or reverse the main course of the pathophysiological process. For example, the increase in vascular permeability, a fundamental phenomenon in trauma, anaphylaxis, or endotoxemia, might be mediated by PAF, LTs, PGs, peptides (e.g. kinins, substance P, CGRP) and amines (e.g. histamine in some species). Attempting to reverse such a complex phenomenon by blocking one specific factor might not be productive unless the specific substance played a key role in generation of the other factors. It seems, however, that while interactions between PGs, LTs, and PAF do occur (31, 32, 70), none of the shock states are crucially dependent on one class of the vasoactive lipids. Therefore, the therapeutic strategy should be based on multiple sites of action, either by drug com-

binations or multiple actions of a specific drug. Such therapy will ultimately provide better protection in the complex situation of shock and trauma, where multiple vasoactive lipids, peptides, and amines act in concert to result ultimately in shock.

Finally, we must remember that none of the synthetic pathways for any of the vasoactive lipids (PGs, TXA_2, or PAF) can be blocked by a specific inhibitor; none of these vasoactive lipids has a highly potent and selective antagonist. The available receptor antagonists or synthesis inhibitors possess multiple sites of action along the arachidonate cascade or pathways of phospholipid metabolism. They also have various pharmacological actions unrelated to the arachidonate cascade. Until potent and selective antagonists and synthesis inhibitors are developed, the interpretation of results obtained by less selective compounds may be misleading.

Literature Cited

1. Bult, A., Herman, A. G. 1982. Prostaglandins and circulating shock. In *Cardiovascular Pharmacology of the Prostaglandins,* ed. P. M. Vanhoutte, H. Denolin, A. Goosens, A. G. Herman, pp. 327–45. New York: Raven
2. Fletcher, J. R., Ramwell, P. W. 1980. Prostaglandins in shock: to give or to block. *Adv. Shock Res.* 3:57–66
3. Anderson, F. L., Jubitz, W., Tsagarics, T. J., Kuida, H. 1975. Endotoxin induced prostaglandin E and F release in dogs. *Am. J. Physiol.* 228:410–14
4. Feuerstein, G., DiMicco, J. A., Kopin, I. J. 1981. Effect of indomethacin on blood pressure and plasma catecholamines response to acute endotoxemia. *J. Pharm. Pharmacol.* 33:576–79
5. McKenchnie, K., Furman, B. L., Parratt, J. R. 1985. Metabolic and cardiovascular effects of endotoxin infusion in conscious unrestrained rats: effects of methylprednidolone and BW 755c. *Circ. Shock* 15:205–15
6. Feuerstein, G., Bayorh, M. A., Stull, R., Goldstein, D. S., Zerbe, R. L., et al. 1985. Effects of nafazatrom on cardiovascular sympathetic and endocrine responses to hemorrhagic shock in conscious rats. *Circ. Shock* 17:223–32
7. Feuerstein, G., Golstein, D., Ramwell, P. W., Zerbe, R. L., Lux, W. E., et al. 1985. Cardiorespiratory, sympathetic and biochemical responses to T-2 toxin in the conscious guinea pig and rat. *J. Pharmacol. Exp. Ther.* 232:786–94
8. Lefer, A. M., Araki, H. 1983. Analysis of potential beneficial actions of prostaglandins in traumatic shock. In *Molecular and Cellular Aspects of Shock and Trauma,* ed. A. M. Lefer, W. Schumer, pp. 199–210. New York: Liss
9. Halushka, P. V., Reines, D., Barrow, S. E., Blair, I. A., Dollery, C. T., et al. 1985. Elevated plasma 6-keto-prostaglandin $F_{1\alpha}$ in patients in septic shock. *Crit. Care Med.* 13:451–53
10. Feuerstein, G., Jimerson, D. C., Kopin, I. J. 1981. Prostaglandins, catecholamines and cardiovascular responses to hemorrhage. *Am. J. Physiol.* 240:R166–74
11. Krausz, M. M., Utsunomuija, T., Feuerstein, G., Wolfe, J. H. N., Shepro, D., et al. 1981. Prostacyclin reversal of lethal endotoxemia in dogs. *J. Clin. Invest.* 67:1118–25
12. Feuerstein, G., Zerbe, R. L., Meyer, D. K., Kopin, I. J. 1982. Alteration of cardiovascular, neurogenic and humoral responses to acute hypovolemic hypotension by administered prostacyclin. *J. Cardiovasc. Pharmacol.* 4:246–53
13. Machiedo, G. W., Warden, M. J., LoVerme, P. J., Rush, B. F. Jr. 1982. Hemodynamic effects of prolonged infusion of prostaglandin E_1 (PGE_1) after hemorrhagic shock. *Adv. Shock Res.* 8:171–76
14. Rao, P. S., Cavanagh, D., Mardsen, K. A., Knuppel, R. A., Spaziani, E. 1984. Prostaglandin D_2 in canine endotoxic shock. Hemodynamic, hematologic, biochemical and blood gas analysis. *Am. J. Obstet. Gynecol.* 148:964–72
15. Northover, B. J., Subramanian, G. 1962. Analgesic antipyretic drugs as an-

tagonists of endotoxin shock in dogs. *J. Pathol. Bacteriol.* 83:463–68
16. Feuerstein, G., Feuerstein, N., Gimmon, Z. 1980. The effect of indomethacin on blood pressure, catecholamines and renin response to acute hemorrhage. In *Advances in Prostaglandins, Thromboxane and Leukotriene Research,* ed. B. Samuelsson, P. W. Ramwell, R. Paoletti, 7:829–33. New York: Raven
17. Perbeck, L., Hedgvist, P. 1980. Prostaglandin E_1 and E_2 antagonize indomethacin induced decrease in survival rate of hemorrhagically shocked rats. *Acta Clin. Scand.* 500:91–94
18. Cook, J. A., Wise, W. C., Halushka, P. V. 1980. Elevated thromboxane levels in the rat during endotoxic shock. *J. Clin. Invest.* 65:227–30
19. Hock, C. E., Lefer, A. M. 1984. Beneficial effect of thromboxane synthetase inhibitor in traumatic shock. *Circ. Shock* 14:159–68
20. Reines, H. D., Halushka, P. V., Cook, J. A., Wise, W. C., Rambo, W. 1982. Plasma thromboxane concentrations are raised in patients dying with septic shock. *Lancet* 2:174–75
21. Lefer, A. M. 1985. Eicosanoid as mediators of ischemia and shock. *Fed. Proc.* 44:275–80
22. Bunting, S., Castro, S., Salmon, J. A., Moncada, S. 1983. The effect of cyclooxygenase and thromboxane synthetase inhibitors on shock induced by injection of heterologous blood in cats. *Thromb. Res.* 30:609–17
23. Armstrong, R. A., Jones, R. L., Wilson, N. H. 1985. Effect of the thromboxane receptor antagonist EP 092 on endotoxin shock in the sheep. *Prostaglandins* 29:703–13
24. Araki, H., Lefer, A. M., Smith, J. B., Nicolau, K. C., Magdda, R. I. 1980. Beneficial actions of a new thromboxane analog in traumatic shock. See Ref. 16, pp. 835–38
25. Anderegg, K., Anzeveno, P., Cook, J. A., Halushka, P. V., McCarthy, J., et al. 1983. Effect of a pyridine derivative thromboxane synthetase inhibitor and its inactive isomer in endotoxic shock in the rat. *Br. J. Pharmacol.* 18:725–32
26. Halushka, P. V., Cook, J. A., Wise, W. C. 1983. Beneficial effects of UK 32748, a thromboxane synthetase inhibitor in experimental endotoxic shock in the rat. *Br. J. Clin. Pharmacol.* 15:1335–95
27. Lefer, A. M., Okamutsu, S., Smith, E. F., Smith, B. 1981. Beneficial effects of a new thromboxane synthase inhibitor in arachidonate-induced sudden death. *Thromb. Res.* 23:265–73
28. Fletcher, J. R., Short, B. L., Casey, L. C., Walker, R. I., Gardiner, H., et al. 1983. Thromboxane inhibition in gram negative sepsis fails to improve survival. In *Advances in Prostaglandins, Thromboxane and Leukotriene Research,* ed. B. Samuelsson, R. Paoletti, P. W. Ramwell, 12:117–30. New York: Raven
29. Casey, L. C., Fletcher, J. R., Zmudea, M. I., Ramwell, P. W. 1982. Prevention of endotoxin induced pulmonary hypertension in primates by use of a selective thromboxane inhibitor OKY 1581. *J. Pharmacol. Exp. Ther.* 222: 441–46
30. Samuelsson, B. 1983. Leukotrienes: mediators of immediate hypersensitivity reactions and inflammation. *Science* 220:568–78
31. Piper, P. J. 1982. Pharmacology and biochemistry of leukotrienes. *Eur. J. Respir. Dis.* 122(63):54–61
32. Feuerstein, G. 1985. Autonomic pharmacology of leukotrienes. *J. Auton. Pharmacol.* 5:149–68
33. Hammarstrom, S. 1983. Leukotrienes. *Ann. Rev. Biochem.* 52:355–77
34. Denzlinger, C., Rapp, S., Hagmann, W., Keppler, D. 1985. Leukotrienes as mediators in tissue trauma. *Science* 230:330–32
35. Hagmann, W., Denzlinger, C., Keppler, D. 1985. Production of peptide leukotrienes in endotoxic shock. *FEBS Lett.* 180:309–13
36. Ogletree, M. L., Brigham, K. L., Oates, J. A., Hubbard, W. C. 1982. Increased flux of 5-HETE production in sheep lung lymph during pulmonary leukostasis after endotoxin. *Fed. Proc.* 40:767 (Abstr.)
37. Luderitz, T. H., Rietchel, E. T., Schade, U. 1983. Release of leukotrienes from macrophages stimulated by lipopolysaccharide endotoxin. *Immunology* 165:213–313
38. Denzlinger, C., Guhlman, A., Hagmann, W., Scheuber, P. H., Scheyerl, F., et al. 1986. Cysteinyl leukotriens undergo enterohepatic circulation. *Prostaglandin Leukotriene Med.* 21:321–22
39. Foster, A., Fitzsimmons, B., Letts, C. G. 1986. The synthesis of *N*-acetyl-leukotriene E_4 and its effects on cardiovascular and respiratory function of the anesthetized pig. *Prostaglandins* 31:1077–86
40. Eimerl, J., Siren, A.-L., Feuerstein, G. 1986. Regional vascular effects of cys-

teinyl leukotrienes. *Am. J. Physiol.* In press
41. Kamitani, T., Little, M. H., Ellis, F. F. 1985. Effect of leukotrienes, 12-HETE, histamine, bradykinin and 5-hydroxytryptamine on in vivo rabbit cerebral arteriolar diameter. *J. Cereb. Blood Flow Metab.* 5:554–59
42. Secrest, R. J., Olsen, E. J., Chapnick, B. M. 1985. Leukotriene D_4 relaxes canine renal and superior mesenteric arteries. *Circ. Res.* 57:323–29
43. Berkowitz, B. A., Zabko Potapovich, B., Valocik, R., Gleason, J. G. 1984. Effect of leukotrienes on the vasculature and blood pressure of different species. *J. Pharmacol. Exp. Ther.* 229:105–12
44. Zukowska-Grojec, Z., Feuerstein, G. 1985. Leukotrienes and shock. In *Leukotrienes in Cardiovascular and Pulmonary Function*, ed. A. M. Lefer, pp. 101–13. New York: Liss
45. Hagmann, W., Denzlinger, C., Keppler, D. 1984. Role of peptide leukotrienes and their hepatobiliary elimination in endotoxin action. *Circ. Shock* 14:223–35
46. Cook, J. A., Wise, W. C., Halushka, P. V. 1985. Protective effect of a selective leukotriene antagonist in endotoxemia in the rat. *J. Pharmacol. Exp. Ther.* 235:470–74
47. Hock, C. E., Lefer, A. M. 1985. Protective effects of a new LTD_4 antagonist (LY-171,883) in traumatic shock. *Circ. Shock* 17:263–72
48. Levine, L. 1983. Inhibition of the A-23187 stimulated leukotriene and prostaglandin biosynthesis of rat basophil leukemia (RBL-1) cells by non-steroid anti-inflammatory drugs, antioxidants and calcium channel blockers. *Biochem. Pharmacol.* 32:3023–26
49. Lux, W. E., Feuerstein, G., Faden, A. I. 1983. Alteration of leukotriene D_4 hypotension by thyrotropin-releasing hormone. *Nature* 302:822–24
50. Benveniste, J., Henson, P. M., Cochrane, C. G. 1972. Leukocyte-dependent histamine release from rabbit platelets: the role of IgE, basophils and a platelet activating factor. *J. Exp. Med.* 136:1356–77
51. Demopoulos, C. A., Pickard, R. N., Hanahan, D. J. 1979. Platelet activating factor: evidence for 1-O-alkyl-2-acetyl-*sn*-glyceryl-3-phosphocholine as the active component (a new class of lipid chemical mediator). *J. Biol. Chem.* 254: 9355–58
52. Blank, M. L., Snyder, F., Byers, L. W., Brooks, B., Muirhead, E. E. 1979. Antihypertensive activity of an alkyl ether analog of phospholidylcholine. *Biochem. Biophys. Res. Commun.* 90: 1194–1200
53. Snyder, F. 1985. Chemical and biochemical aspects of platelet activating factor: a novel class of acetylated ether linked choline phospholipids. *Med. Res. Rev.* 5:107–40
54. Benveniste, J. 1985. PAF-acether (platelet activating factor). *Advances in Prostaglandin, Thromboxane and Leukotriene Research* 13:11–18. New York: Raven
55. Voelkel, N. F., Worten, S., Reeves, J. T., Henson, P. M., Murphy, R. C. 1982. Nonimmunological production of leukotrienes induced by platelet activating factor. *Science* 218:286–89
56. Feuerstein, G., Zukowska-Grojec, Z., Krausz, M. M., Blank, M. L., Snyder, F., et al. 1982. Cardiovascular and sympathetic effects of 1-O-hexadecyl-2-acetyl-*sn*-glycero-3-phosphorylcholine in conscious SHR and WKY rats. *Clin. Exp. Hypertension* A4:1335–50
57. Feuerstein, G., Lux, W. E. Jr., Ezra, D., Hayes, E. C., Snyder, F., et al. 1985. Thyrotropin releasing hormone blocks the hypotensive effect of platelet activating factor in unanesthetized guinea pig. *J. Cardiovasc. Pharmacol.* 7:335–40
58. Bessin, P., Bonnet, J., Apffel, D., Soulard, C., Desgroux, L., et al. 1983. Acute circulating collapse caused by platelet activating factor (PAF acether) in dogs. *Eur. J. Pharmacol.* 86:403–13
59. Goldstein, R. E., Laurindo, F. R. M., Ezra, D., Feuerstein, G. 1987. Mechanism of circulating collapse induced by PAF-acether. In *Lipid Mediators in Immunology of Burn and Sepsis*, ed. M. Braquet. New York: Plenum. In press
60. Feuerstein, G., Boyd, L. M., Ezra, D., Goldstein, R. E. 1983. Effect of platelet activating factor on coronary circulation of the domestic pig. *Am. J. Physiol.* 246:H466–71
61. Sybertz, E. J., Watkins, R. W., Baum, T., Pula, K., Rivelli, M. 1984. Cardiac, coronary and peripheral vascular effects of acetyl ether phosphoryl choline in the anesthetized dog. *J. Pharmacol. Exp. Ther.* 232:156–62
62. Levi, R., Burke, J. A., Guo, Z. G., Hattori, Y., Hoppens, C. M., et al. 1984. Acetyl glyceryl ether phosphorylcholine (AGEPC): a putative mediator of cardiac anaphylaxis. *Circ. Res.* 54:117–24

63. Camussi, G., Aglietta, M., Malavasi, F., Tetta, C., Piacibelo, W., et al. 1983. The release of platelet activating factor from human endothelial cells in culture. *J. Immunol.* 131:2397–403
64. Benveniste, J., Boullet, C., Brink, C., Labat, C. 1983. The actions of PAF acether (platelet activating factor) on guinea pig isolated heart preparation. *Br. J. Pharmacol.* 80:81–83
65. Cervoni, P., Herzlinger, H. E., Lai, F. M., Tanikella, T. K. 1983. Aortic vascular and atrial responses to (±) 1-O-octa-decyl-2-acetyl-glycero-3-phosphocholine. *Br. J. Pharmacol.* 79: 667–71
66. Doebber, T. W., Wu, M. S., Robbins, J. C., Choy, B. M., Chang, M. N., et al. 1985. Platelet activating factor (PAF) involvement in endotoxin induced hypotension in rats; studies with PAF-receptor antagonist kadsurenone. *Biochem. Biophys. Res. Commun.* 127: 799–808
67. Inarrea, P., Gomez-Cambronero, J., Pascual, J., del Carmen-Ponte, M., Hernando, L., et al. 1985. Synthesis of PAF acether and blood volume changes in gram negative sepsis. *Immunopharmacology* 9:45–52
68. Terashita, Z., Imura, Y., Nishikawa, K., Sumida, S. 1985. Is platelet activating factor (PAF) a mediator of endotoxin shock? *Eur. J. Pharmacol.* 109:257–61
69. Etienne, A., Hecquet, F., Soulard, C., Spinnewy, B., Clostre, F., et al. 1985. In vivo inhibition of plasma protein leakage and *Salmonella enteritidis*–induced mortality in the rat by specific PAF acether antagonist BN 52021. *Agents Actions* 17:368–70
70. Braquet, P., Touqui, L., Varagaftig, B. B., Sheh, T. Y. 1986. Perspectives in platelet activating factor research. *Pharmacol. Rev.* In press
71. Darius, H., Lefer, D. J., Smith, B., Lefer, A. M. 1986. Role of platelet activating factor-acether in mediating guinea pig anaphylaxis. *Science* 232:58–60