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INCREASED PLASMA LEVELS OF LEUKOTRIENE B4 AND PROSTAGLANDIN E2 IN CATS EXPERIMENTALLY INOCULATED WITH FELINE INFECTIOUS PERITONITIS VIRUS

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ABSTRACT

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Specific-pathogen-free kittens experimentally infected with feline infectious peritonitis virus (FIPV) subsequently demonstrated increased plasma levels of the arachidonic acid metabolites, leukotriene (LT) B4 and prostaglandin (PG) E2. Significant increases ($P<0.025$) in LTB4 plasma levels occurred in all (5/5) FIPV-inoculated kittens on postchallenge-exposure days (PCD) 7 and 14 vs PCD 0. Significant increases ($P<0.05$) in PGE2 plasma levels occurred in 80% (4/5) of FIPV-infected kittens on PCD 7 and 14. Maximal mean plasma levels of LTB4 and PGE2 occurred on PCD 7 (502.5±45.6 pg/ml and 1108.0±247.9 pg/ml, respectively). A positive correlation was found between LTB4 plasma levels and body temperature ($r = 0.609$, $P<0.01$). Mean survival time in FIPV-inoculated kittens was 19.4±3.2 days. Gross lesions, including peritoneal or pleural effusions (or both) and connective tissue edema, indicated an increased vascular permeability in the FIPV-infected kittens. Histologically, lesions were characterized by vasculitis or perivasculitis, vasodilatation, perivascular edema, and fibrinonecrotizing and pyogranulomatous inflammation. Immunofluorescent studies of tissues from FIPV-infected kittens demonstrated foci of polymorphonuclear leukocytes and FIPV-positive macrophages oriented around dilated blood vessels. Seemingly, arachidonic acid metabolites, including LTB4 or PGE2 released from macrophages, neutrophils or other cells, may be involved in the pathogenesis of FIP vascular and inflammatory lesions and in some of the clinical disease manifestations.

INTRODUCTION

Feline infectious peritonitis (FIP) is a progressive and fatal immune-mediated coronaviral disease of cats (Pedersen, 1985; August, 1984). The pathologic lesions in FIP are detailed in numerous reports (Wolfe & Griesemer, 1971; Holmberg & Gribble, 1973; Montali & Strandberg, 1972; Slausen & Finn, 1972; Weiss & Scott, 1981b) and consist of vasculitis and perivascular pyogranulomatous or fibrinonecrotizing inflammation (or both) in serosae and visceral organs. Clinically, FIP-diseased cats can have a chronic fluctuating fever and develop variable amounts of peritoneal or pleural fluid (or both). The fluids are exudates containing mostly fibrin and other serum proteins, macrophages, and neutrophils (Pedersen, 1983; 1985; Barlough & Weiss, 1983).

The pathophysiologic mechanisms responsible for FIP lesions are not well understood. Loss of fluid and other plasma constituents from inflamed blood vessels, immunologically damaged by complexes of virus, antiviral antibodies and complement (C) proteins (August, 1984; Barlough & Weiss, 1983; Pedersen & Boyle, 1980; Weiss & Scott, 1981c; Jacobse-Geels *et al.*, 1982) or by cytotoxic lymphokines or other enzymatically-active

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factors released during cellular immune responses (Pedersen, 1985), may occur in cases of acute FIP. Except for studies of C3 fragments (Pedersen & Boyle, 1980; Weiss & Scott, 1981c; Jacobse-Geels *et al.*, 1980; 1982) and a recent report on interleukin (IL)-1 (Goitsuka *et al.*, 1987), there are presently no reports of biochemical mediators of inflammation involved in FIP.

Inflammatory mediators such as leukotrienes (LT) and prostaglandins (PG), both of which are fatty acid metabolites of arachidonic acid (AA), can be synthesized in cell membranes and subsequently released after cellular activation or injury (Gerrard, 1985a). Various pharmacologic actions, including increased vascular permeability, edema, vasomotor changes, neutrophil and macrophage chemotaxis, or fever production, are associated with their release (Piper, 1984; Parker, 1984; Wolfe & Coceani, 1979). Additionally, PGE2 can suppress specific cellular (T-cell) immune responses (Rocklin *et al.*, 1980). Although several kinds of cells, including leukocytes, platelets, endothelial cells, smooth muscle cells and fibroblasts, can be stimulated to synthesize LT or PG, macrophages and neutrophils are apparently the major sources (Parker, 1984; Gerrard, 1985b; Gordon, 1985). Macrophages and neutrophils are also the predominant cells in FIP inflammatory lesions; and macrophages are frequently infected by FIPV (Pedersen, 1983; 1985; Weiss & Scott, 1981b; Barlough & Weiss, 1983).

The objectives of the present study were to measure the plasma concentrations of LTB4 and PGE2 in specific-pathogen-free (SPF) kittens before and after experimental infection with FIPV and to suggest a role of AA metabolites in the pathogenesis of FIP.

MATERIALS AND METHODS

Animals

The SPF kittens used in this study were purchased from a commercial breeding colony (Liberty Laboratories, Liberty Corners, NJ) at 14- to 16-weeks-old. The kittens were housed in individual cages and were maintained at the Auburn University Animal Isolation Facility. All the kittens were test negative (by immunofluorescence) for feline leukemia virus and were test negative for feline coronavirus serum antibodies (by virus neutralization). The FIPV challenge-exposed and nonchallenged-exposed control kittens were housed in separate isolation rooms.

Virus

The DF2 strain of FIPV (ATCC No VR-2004, American Type Culture Collection, Rockville, MD) was used both for virus challenge-exposure and also as target virus for FIPV antibody assays. The virus was passed 6 times in CrFk cells (obtained from Dr L. Swango, Auburn, AL) in our laboratory, concentrated by ultrafiltration (Minitan™ System, Millipore, Bedford, Mass), and stored in tissue culture growth media (1-ml aliquots) at −80°C until use. The titer of the FIPV was approximately $10^{7.3}$ tissue culture infective doses ($TCID_{50}$) per ml. By titration, it was determined that the inoculum contained approximately $10^{4.8}$ cat lethal doses (LD_{100}) per ml.

Experimental design

Each of five kittens was inoculated intraperitoneally (IP) with approximately 50 LD_{100} of FIPV on postchallenge-exposure day (PCD) 0. Two additional kittens were inoculated with growth media only (age-matched nonchallenge-exposed controls). On PCD 0, 7, 14, 21 and 28 the kittens were mildly sedated with ketamine HCl (Vetalar™, Parke, Davis &

Co, Detroit, MI) given intramuscularly (10 mg/kg) and blood samples were collected from the external jugular vein into vacuum-evacuated blood collection tubes (Vacutainer™, Becton Dickinson & Co, Columbus, NB). Plasma or serum was processed for LTB4 and PGE2 determinations, or for virus neutralizing antibody assays, respectively. Rectal temperatures and clinical signs of disease were monitored daily. Complete gross necropsy examinations were performed on all the kittens and samples were taken for histopathologic examinations and immunofluorescent studies. Control kittens were euthanatized and necropsied on PCD 42.

Radioimmunoassasy (RIA) determinations of plasma LTB4 and PGE2

Levels of LTB4 or PGE2 in plasma were determined using RIA and liquid scintillation techniques. Pilot studies using human RIA reagents for LTB4 or PGE2 determinations in feline plasma samples showed good reproducibility, accuracy, and sensitivity. Plastic pipettes and tubes (Sarstedt, Princeton, NJ) were used for all sample preparations and RIA procedures. Three ml of blood from each kitten was collected into evacuated tubes containing K_3 EDTA and centrifuged at 1000 × g for 10 minutes at 5°C. The plasma was removed, frozen, and stored at −80°C until used. Before RIA analysis, LTB4 and PGE2 were extracted from plasma. Briefly, 0.1 ml HCl (0.1 N) was added to 1.0 ml plasma to acidify the samples. This mixture was vortexed and 3.0 ml ethylacetate was added. The mixture was vortexed twice for 20 seconds each. The sample was centrifuged at 500 × g for 10 minutes at 5°C. The supernatant was removed and dispensed into tubes containing equal 1.4 ml portions for LTB4 or PGE2 analysis. The ethylacetate extracts were placed in a water bath at 37°C and blown to dryness under a stream of nitrogen gas. The residues were resuspended in 0.25 ml of LTB4 or PGE2 buffer supplied with the respective RIA kit (LTB4 RIA Kit, New England Nuclear, Boston, Mass; PGE2 RIA Kit, Seragen, Boston, Mass) and were stored at −80°C until used. On the day of assay, the samples were thawed, vortexed, centrifuged at 500 × g for 5 minutes at 5°C, and placed on ice until assayed.

For LTB4 or PGE2 determinations, 0.1 ml aliquots of extracted plasma samples were assayed in duplicate using the respective RIA kit and procedure outlined in the manufacturer's protocol. Briefly, test samples or standard solutions containing unlabelled LTB4 or PGE2 were incubated with diluted antibodies and radiolabelled ligands for 18 hours at 4°C. Bound fractions were separated after addition of dextran-coated charcoal followed by centrifugation at 2000 × g for 15 minutes at 5°C. The supernatants were removed and transferred into 7-ml scintillation vials, and 5-ml of scintillation fluid (Scinti Verse II™, Fischer Scientific Co, Fairlawn, NJ) was added to each vial. The vials were vortexed for 20 seconds and the radioactivity in each vial was determined using a liquid scintillation counter (LS 7000, Beckman Instruments Inc, Irvine, CA). The levels of LTB4 or PGE2 in the extracted samples were determined by interpolation from their respective standard curves.

Virus neutralizing antibody (VNA) assay

For VNA assays, blood was collected into evacuated tubes without anticoagulant and stored overnight at room temperature. The blood was centrifuged at 800 × g for 20 minutes and the supernatants were dispensed into 1-ml portions, frozen, and stored at −80°C until use. Serum VNA titers to FIPV-DF2 were determined using a standard infectivity inhibition-type assay in feline embryo (fcwf-4) cells (obtained from Dr NC Pedersen, Davis, CA). This assay was performed essentially as described by Pedersen &

Black (1983), except that 50 $TCID_{50}$ of FIPV were incubated with each dilution of serum and cytopathic effects (CPE) were scored at 48 hours. Serum VNA titers were recorded as the reciprocal of the highest dilution of serum that inhibited CPE in 50% of test wells.

Necropsy Examination

All kittens were examined for gross lesions. Representative sections of all organs and lesions were fixed in 10% neutral buffered formalin. The fixed tissues were embedded in paraffin, sectioned at 6 μm, stained with hematoxylin and eosin (H & E) and examined by light microscopy.

For immunofluorescent (IF) studies, 1-cm^2 pieces of liver were frozen by immersion in liquid nitrogen and stored at −80°C until use. Frozen tissues were cryosectioned at 8 μm, fixed in acetone for 10 minutes at −20°C and then stored at −20°C until use. Indirect fluorescent antibody (FA) tests for detection of FIPV antigens in tissues were performed as previously described (Weiss & Scott, 1981a). Samples were examined with an epi-fluorescent ultraviolet light microscope (IMT-2, Olympus Corp, Lake Success, NY).

Statistical tests

Analysis of data was performed using a computerized statistical analysis program (Stat Pak Gold™, Walonick Assoc, Minneapolis, MN). Correlations between body temperatures in FIPV challenge-exposed kittens and corresponding LTB4 or PGE2 plasma levels were determined by simple linear regression analysis. A 1-way analysis of variance and 1-tailed Student's t test were used to determine significant ($P<0.05$) differences between LTB4 or PGE2 mean plasma levels before and at weekly intervals after FIPV challenge-exposure.

RESULTS

Clinical and serological responses

All FIPV challenge-exposed kittens demonstrated an initial increase (range, 1.5 to 2.0°C) in rectal temperature on PCD 2. The initial febrile response was transient, lasting only 24 to 48 hours before body temperature returned to normal levels. The maximal temperatures on PCD 2 or 3 ranged between 39.3 and 40.4°C. A second and more sustained increase in body temperature occurred after 1 to 2 weeks, or about 7 to 10 days before death. Mucous membrane pallor, icterus, anorexia, central nervous system depression, dyspnea and occasionally melena accompanied the fever. Subnormal body temperatures were present 24 to 48 hours before death. Mean survival time ± standard deviation (SD) and range (min-max) were 19.4±3.2, 17 to 25 days.

Virus neutralizing serum antibodies against FIPV were either not detected (cats 2 and 5) or were present only at low concentrations (cats 1, 3 and 4) on PCD 7. Primary antibody responses in cats 2 and 5 occurred between PCD 7 and 14. Antibody titers in all FIPV challenge-exposed kittens increased rapidly after PCD 7 and VNA titers on PCD 14 ranged from 640 to 7 680 (Table 1). Age-matched nonchallenged control kittens ($n = 2$) did not demonstrate VNA in their sera on PCD 0, 7, 14, 21 or 28 and did not show fever or other signs of disease.

Plasma LTB4 and PGE2 levels

Increased levels of LTB4 and PGE2 were detected in the plasma of kittens after

TABLE I
Mean rectal temperatures, leukotriene (LTB4) and prostaglandin (PGE2) plasma levels, and serum antibody titers in feline infectious peritonitis virus (FIPV)-inoculated or noninoculated control kittens

Group	PCD	Rectal temperature (C)	LTB4 (pg/ml)	PGE2 (pg/ml)	Serum VNA titer*
FIPV-	0	38.4±0.4	365.5±63.3	900.5±81.0	neg
inoculated	7	39.6±0.6	502.5±45.6‡	1108.0±247.9	neg to 60
kittens (n = 5)	14	39.5±0.5	489.5±102.7‡	1053.5±146.0	640 to 7,680
	21+	40.1	458.8±150.3	743.8±323.5	1,920 to 3,840
Noninoculated	0	38.5±0.8	320.0±21.2	915.0±42.4	neg
control kittens	7	38.7±0.4	333.8±15.9	881.3±76.0	neg
(n = 2)	14	39.2±0.4	342.5±42.4	810.0±63.6	neg
	21	38.9±0.8	310	702.5±70.7	neg

* Reciprocal of serum dilution, reported as range of titers within group; + n = 2.
‡ Significant increase in mean LTB4 plasma levels vs PCD 0, $P<0.025$.
PCD = postchallenge-exposure day; VNA = virus neutralizing antibody; neg = negative at 1:10 serum dilution.
Rectal temperatures, LTB4, and PGE2 levels expressed as mean ± SD.

challenge-exposure to FIPV. Compared to mean plasma levels on PCD 0, LTB4 levels in FIPV challenge-exposed kittens were significantly increased on PCD 7 ($P<0.01$) and also on PCD 14 ($P<0.025$); maximal increases occurred on PCD 7 (cats 1, 2 and 3) or on PCD 14 (cats 4 and 5) (Figure 1). In cats 1 and 2, LTB4 levels rapidly declined after the peak response on PCD 7; cats 4 and 5, however, demonstrated increased LTB4 levels throughout the disease. Mean plasma levels ± SD of LTB4 in all FIPV challenge-exposed kittens were increased on PCD 7, 14 and 21 compared to mean plasma levels of LTB4 in age-matched control kittens sampled on the same days (502.5±45.6, 489.5±102.7, and 458.8±150.3 pg/ml vs 333.8±15.9, 342.5±42.4, and 310.0 pg/ml, respectively) (Table 1).

Plasma levels of PGE2 were increased in 4 out of 5 kittens after FIPV challenge-exposure (Figure 2). Mean PGE2 plasma levels in these 4 kittens were significantly increased on PCD 7 ($P<0.05$) and also on PCD 14 ($P<0.005$) compared to mean plasma PGE2 levels on PCD 0. In cat 2, plasma PGE2 levels decreased after FIPV challenge-exposure. In individual kittens, maximal plasma PGE2 levels (962.5 to 1 507.5 pg/ml) occurred on PCD 7 or 14. Mean ± SD plasma PGE2 levels in all FIPV challenge-exposed kittens were increased on PCD 7 and 14 vs levels in age-matched control kittens (1108.0±247.9 and 1053.5±146.0 pg/ml vs 881.3±76.0 and 810.0±63.6 pg/ml, respectively) (Table 1).

Maximal increases in mean LTB4 or PGE2 plasma levels occurred in FIPV challenge-exposed kittens on PCD 7. At this time, kittens had demonstrated febrile responses (mean ± SD, 39.6±0.6 C) and serum antibodies were either not detected or were present only at low concentrations (Table 1). A significant positive correlation ($r = 0.609$; 15 df, $P<0.01$) was found between LTB4 plasma levels and body temperature (Figure 3). A correlation between plasma PGE2 levels and body temperature, however, was not observed ($r = 0.043$; 15 df, $P>0.8$) (Figure 4).

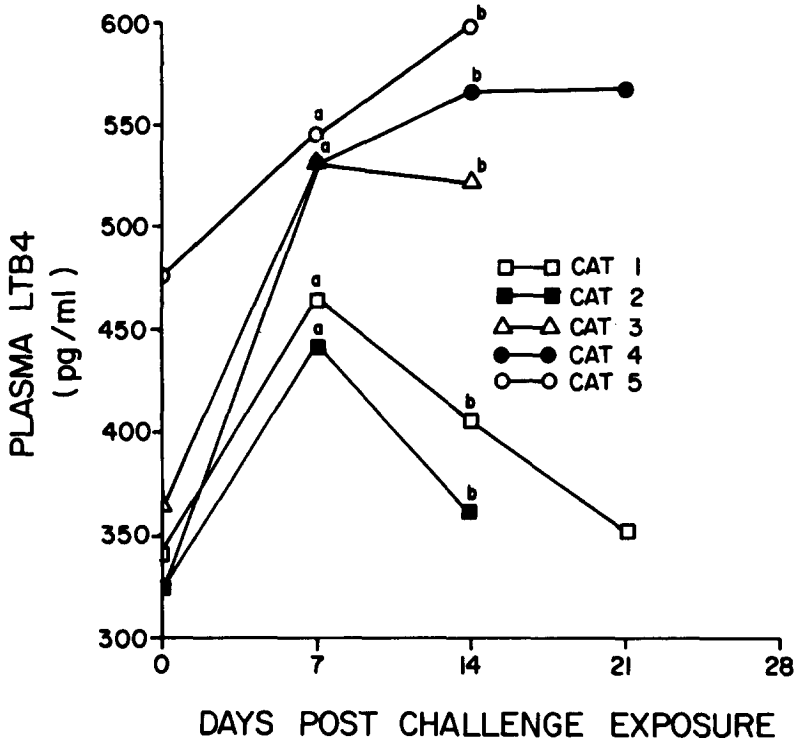

Figure 1. Plasma levels of leukotriene B4 (LTB4) in SPF kittens challenge-exposed to FIPV. [a]Significant ($P<0.01$) increase in mean LTB4 plasma levels on postchallenge-exposure day (PCD) 7 vs PCD 0 ($n=5$); [b]Significant ($P<0.025$) increase in mean LTB4 plasma levels on PCD 14 vs PCD 0 ($n=5$).

Gross and microscopic findings

Gross lesions in FIPV challenged-exposed kittens appeared as disseminated 0.5 to 10.0 mm white foci in liver, omentum, spleen, kidney, lungs, visceral and parietal peritoneum, intestines, pancreas and mesenteric, ileo-cecal and sternal lymph nodes. The foci were frequently oriented around superficial veins. Clear yellow, viscous peritoneal or pleural fluid containing fibrin strands was present in most kittens. The fluid ranged from several ml to more than 30 ml in volume. The mesentery, omentum, mediastinal tissue, and mesenteric lymph nodes were frequently edematous. Mesenteric and sternal lymph nodes were enlarged. Several kittens demonstrated thymic atrophy.

Microscopic lesions consisted of disseminated foci of fibrinonecrotic or pyogranulomatous inflammation predominantly in the parietal peritoneum and serosae, liver, spleen, pancreas, visceral lymph nodes, thymus, kidneys, and leptomeninges. The lesions were oriented around small veins as perivenous infiltrates of macrophages, neutrophils, small lymphocytes, fibrin, and nuclear debris. The inflammatory cell infiltrates were frequently located around dilated blood vessels in edematous areas of mesentery, intestinal serosa or omentum. Gross or microscopic changes were not observed in tissues from nonchallenge-exposed control kittens.

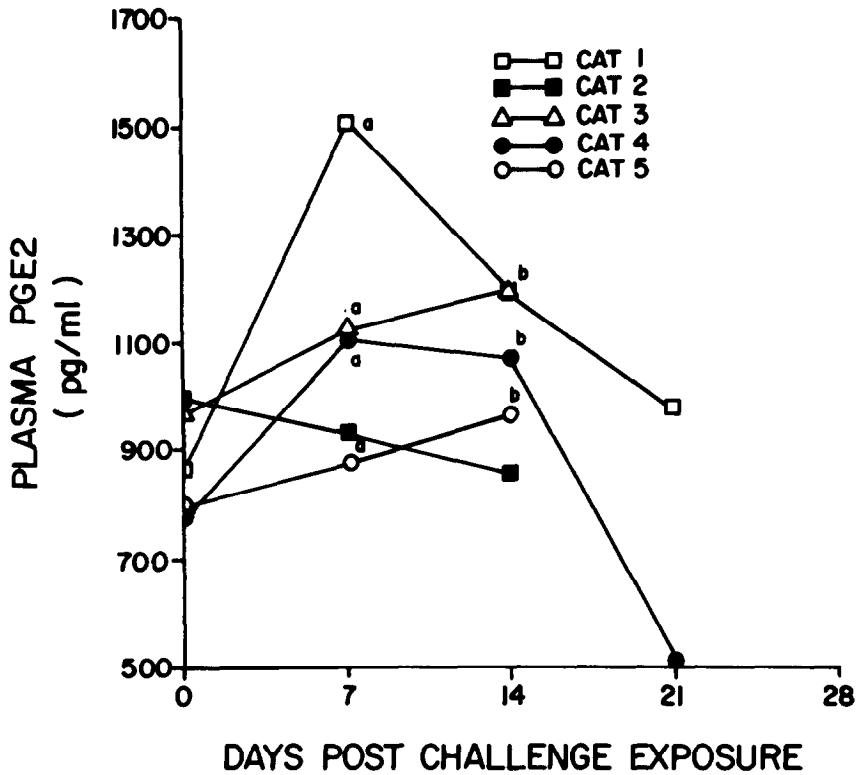

Figure 2. Plasma levels of prostaglandin E2 (PGE2) in SPF kittens challenge-exposed to FIPV. [a]Significant ($P<0.05$) increase in mean PGE2 plasma levels on postchallenge-exposure day (PCD) 7 vs PCD 0 ($n = 4$); [b]Significant increase in mean PGE2 plasma levels on PCD 14 vs PCD 0 ($n = 4$).

Immunofluorescent studies

Indirect FA tests on frozen sections of liver from FIPV challenge-exposed kittens demonstrated specific antiviral fluorescence. The fluorescent foci were frequently in periportal areas or near the capsule. Scattered FIPV-positive cells also were in sinusoids. The antiviral fluorescence was observed as diffuse or granular patterns in the cytoplasm of large, pleomorphic mononuclear cells resembling macrophages. Infected cells were often around blood vessels, the latter frequently dilated veins or small arteries. FIPV-positive mononuclear cells were occasionally within the lumen, attached to the intimal surface or loosely scattered within or around the adventitia of hepatic blood vessels. The FIPV antigens were also detected extracellularly in areas of necrosis infiltrated by polymorphonuclear leukocytes (PMN) and fluorescent mononuclear inflammatory cells. Specific antiviral fluorescence was not observed in liver sections from nonchallenge-exposed control kittens.

DISCUSSION

Kittens experimentally infected with FIPV developed increased plasma levels of the inflammatory mediators LTB4 and PGE2 during the disease. Circulating levels of LTB4

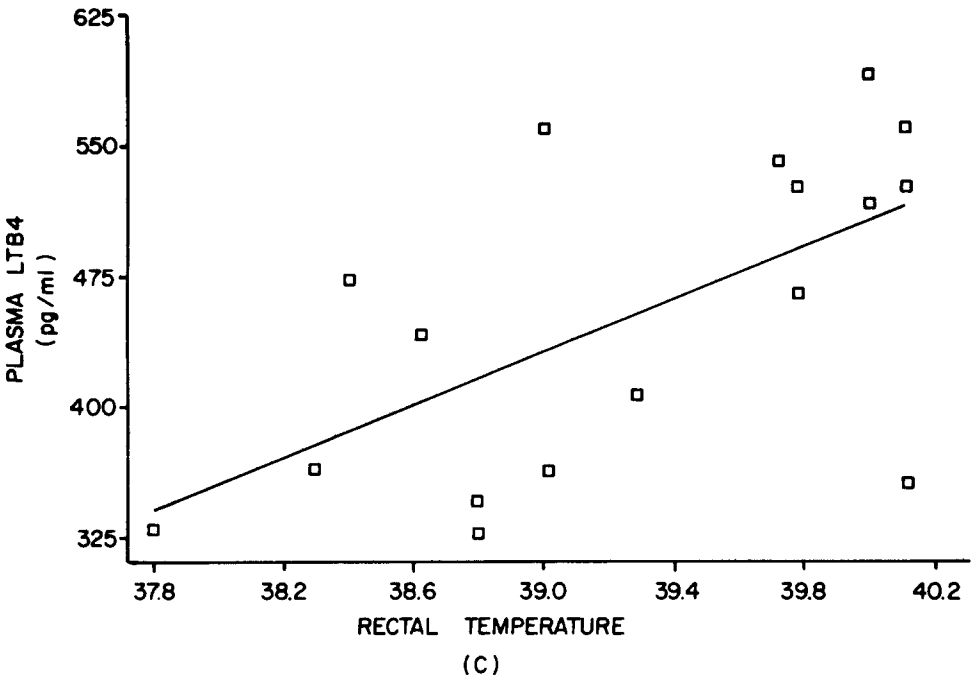

Figure 3. Correlation between plasma LTB4 levels and rectal temperatures in FIPV challenge-exposed kittens, indicating a significant ($P<0.01$) correlation. $Y = 43.26 x + 3988.23$; $r = 0.609$.

and PGE2 were maximal in most kittens within the first week after virus exposure when the kittens were febrile, yet showed minimal serum antibody responses. Subsequently, pathologic and FA examinations of infected kittens demonstrated peritoneal and pleural effusions, tissue edema and disseminated inflammatory reactions characterized by perivascular infiltration of FIPV-infected macrophages and neutrophils, lymphocytes, fibrin and edema fluid.

The pathophysiologic responses of animals to AA metabolites (including LTB4 or PGE2), viz increased vascular permeability, vasodilatation, chemotaxis for neutrophils or monocytes, lysosomal enzyme release and the production of fever (Piper, 1984; Parker, 1984; Wolfe & Coceani, 1979) are consistent with several pathologic findings observed in the FIPV-infected kittens. Major cellular sources of PGE2 and LTB4 are macrophages and neutrophils (Parker, 1984; Gerrard, 1985b), cell-types which predominate in FIP lesions (Weiss & Scott, 1981b). The findings in this study and in a previous study (Weiss & Scott, 1981c) of perivascular edema and infiltrating PMN and FIPV-infected macrophages around blood vessels, suggest that local mediator release plays a role in the pathogenesis of FIP lesions. Synthesis by and release of PGE2 or LTB4 (or both) by perivascular and migrating macrophages and neutrophils could (1) mediate vascular permeability changes, resulting in edema and peritoneal or pleural effusions; and (2) provide additional chemotactic stimuli for neutrophils and monocytes. Seemingly, a vicious cycle might ensue, in which these inflammatory mediators are released from infected or other cells and attract more PMN and viral target cells (viz macrophages). The migrating cells may themselves release additional mediators and also cell-damaging lysosomal enzymes and toxic metabolites of oxygen (free radicals), includ-

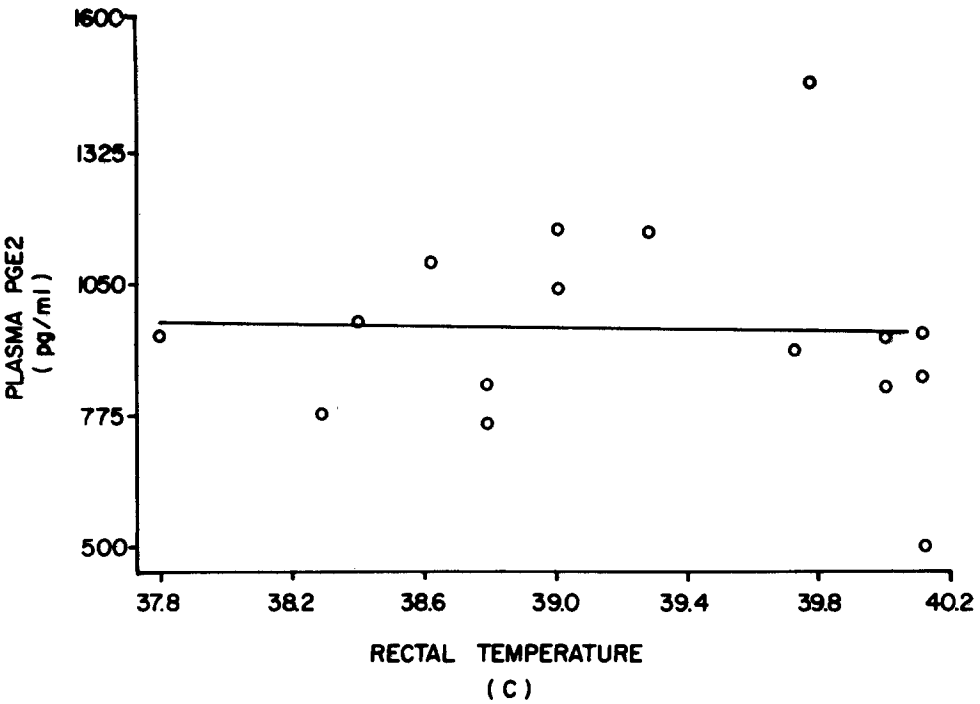

Figure 4 Scattergram of plasma PGE2 levels and rectal temperatures in FIPV challenge-exposed kittens. A correlation between PGE2 levels and rectal temperature was not observed. $Y = -6.86 x + 1686.18$; $r = 0.043$; $P>0.80$.

ing superoxide, hydrogen peroxide, and hydroxy radical (Parker, 1984). The net result would be enhanced local virus production and increased tissue damage.

Although vascular lesions, and possibly the pathologic effusions, in FIP are believed to occur via immunological (antibody-mediated) mechanisms (Pedersen, 1985; August, 1984; Weiss & Scott, 1981b; 1981c), the occurrence of fever and increased plasma levels of LTB4 and PGE2 prior to detectable antibody responses in some FIPV-infected kittens suggest that nonimmunological factors can be involved in some disease manifestations. The immune system, certainly, could amplify initial pathophysiologic responses to FIPV by generating circulating C-activating immune complexes (Jacobse-Geels *et al.*, 1982) or by promoting local cell-mediated reactions and release of lymphokines and other enzymatically-active factors (Pedersen, 1985). The release of certain C fragments, particularly C3a and C5a, can be associated with several vascular effects related previously to AA metabolites, ie increased vascular permeability, granule enzyme release and PMN chemotaxis (Parker, 1984). Indeed, C fragments can also be synthesized in macrophages (Koj, 1985; Colten, 1976). Other investigators have also reported early increases in serum C levels after experimental FIPV infection (Jacobse-Geels *et al.*, 1982). Some of the pathologic changes described in this study may in fact be due to C-activation. It is likely, however, that early vascular disturbances reflect the release of multiple acute phase (AP) proteins, including AA metabolites, C fragments IL-1 and enzymes from infected macrophages or other cells. Thus, local production of AP proteins by macrophages could provide the initial host response to virus invasion.

A positive correlation was found in the present study between plasma LTB4 levels and

temperature responses in FIPV-infected kittens. Although PGE2 or monocyte-derived IL-1 has been associated with the general febrile response (Wolfe & Coceani, 1979; Cebula *et al.*, 1979), there are presently no reports of LTB4 involvement in the pathogenesis of fever. Apparently, the initial step in the pathogenesis of infectious fever is interaction of the pathogen with monocytes or macrophages and, subsequently, elaboration and release of endogenous pyrogen, believed to be IL-1 (Cebula *et al.*, 1979). Indeed, stimulated peritoneal exudate cells from cats with spontaneous FIP produce significant amounts of IL-1 (Goitsuka *et al.*, 1987). Although IL-1 may stimulate PGE2 secretion by macrophage-like cells situated in or near hypothalmic thermoregulatory centers (Stitt, 1986), it is not presently known whether endogenous or exogenous LTB4 is capable of mediating fever. To show this, the LTB4 might have to be inoculated directly into the cerebral vasculature, since blood levels of other molecules such as PGE2 may not reach the hypothalamus in sufficient quantities to produce fever directly (Gerrard, 1985c). The early fever in FIP could also be mediated by interferon (IFN) which, like PGE2, LTB4 or C fragments, may be released by macrophages (Stewart, 1981). FIPV induces increased levels of circulating IFN in kittens within days after experimental infection (Weiss, unpublished data, 1987). Apparently, the synthesis of PGE2 is enhanced by IFN, particularly during virus infections which induce IFN (Stringfellow & Brideau, 1984). Possibly, local IFN-stimulated synthesis and release of PGE2 from brain macrophages could stimulate hypothalamic cells to generate febrile responses (Stitt, 1986).

In addition to the proinflammatory effects of PGE2, the latter may directly enhance the replication of certain viruses and also suppress *in vitro* cytotoxic, suppressor and natural killer cell activities (Parker, 1984; Gerrard, 1985c). Some authors suggest that endogenous macrophage-derived PGE2 may block critical immunoregulatory and antiviral actions mediated by IFN (Stringfellow & Brideau, 1984). If this indeed occurs, viruses like FIPV which infect and damage macrophages may enhance their survival by promoting release of biochemically-active molecules which suppress early host antiviral and protective immune responses. Future studies are needed to define the roles (and interactions) of AA metabolites, IFN and the C-system in FIP pathogenesis and immunity.

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REFERENCES

August, J. R. 1984. Feline infectious peritonitis: An immune-mediated coronaviral vaculitis. *Vet. Clin. North Am. (Small Anim. Pract.)*, **14**, 971–984

Barlough, J. E. & Weiss, R.C. 1983. Feline infectious peritonitis. In: R. W. Kirk (ed). *Current veterinary therapy VIII: Small animal practice.* (W. B. Saunders Co, Philadelphia), 1186–1193

Cebula, T. A., Hanson, D. A., Moore, D. M. *et al.* 1979. Synthesis of four endogenous pyrogens by rabbit macrophages. *J. Lab. Clin. Med.*, **94**, 95–105

Colten, H. R. 1976. Biosynthesis of complement. *Adv Immunol*, **22**, 67–118

Gerrard, J. M. 1985a. *Prostaglandins and leukotrienes: Blood and vascular cell function.* (Marcel Dekker Inc, New York), 3–59

Gerrard, J. M. 1985b. *Prostaglandins and leukotrienes: Blood and vascular cell function.* (Marcel Dekker Inc, New York), 77–207

Gerrard, J. M. 1985c. *Prostaglandins and leukotrienes: Blood and vascular cell function.* (Marcel Dekker Inc, New York), 239–256
Goitsuka, R., Hirota, Y. & Tomoda, I. 1987. Release of interleukin-1 from peritoneal exudate cells of cats with feline infectious peritonitis. *Jpn. J. Vet. Sci.*, **49**, 811-818.
Gordon, A. H. 1985. Responses of connective and other tissue and cell types to injury-derived factors. In: A. H. Gordon and A. Koj (eds). *The acute-phase response to injury and infection.* (Elsevier Press, Amsterdam), 111–119
Holmberg, C. A. & Gribble, D. H. 1973. Feline infectious peritonitis: Diagnostic gross and microscopic lesions. *Feline Pract.*, **4**, 11–14
Jacobse-Geels, H. E. L., Daha, M. R. & Horzinek, M. C. 1980. Isolation and characterization of feline C3 and evidence for the immune complex pathogenesis of feline infectious peritonitis. *J. Immunol.*, **125**, 1606–1610
Jacobse-Geels, H. E. L., Daha, M. R. & Horzinek, M. C. 1982. Antibody, immune complexes and complement activity. Fluctuations in kittens with experimentally induced feline infectious peritonitis. *Am. J. Vet. Res.*, **43**, 666–670
Koj, A. 1985. Extrahepatic synthesis of acute-phase proteins. In: A. H. Gordon and A. Koj (eds). *The acute-phase response to injury and injection.* (Elsevier Press, Amsterdam), 221–226
Montali, R. J. & Strandberg, J. D. 1972. Extraperitoneal lesions in feline infectious peritonitis. *Vet. Pathol.*, **9**, 109–121
Parker, C. W. 1984. Mediators: Release and function. In: W. E. Paul (ed). *Fundamental immunology.* (Raven Press, New York), 697–747
Pedersen, N. C. & Boyle, J. F. 1980. Immunologic phenomena in the effusive form of feline infectious peritonitis. *Am. J. Vet. Res.*, **41**, 868–876
Pedersen, N. C. 1983. Feline infectious peritonitis and feline enteric coronavirus infections. Part 2: Feline infectious peritonitis. *Feline Pract.*, **13**, 5–20
Pedersen, N. C. & Black, J. W. 1983. Attempted immunization of cats against feline infectious peritonitis, using avirulent live virus or sublethal amounts of virulent virus. *Am. J. Vet. Res.*, **44**, 229–234
Pedersen, N. C. 1985. Feline infectious peritonitis. In: R. G. Olsen, S. Krakowka and J. R. Blakeslee (eds). *Comparative pathobiology of viral diseases. Vol 2.* (CRC Press Inc, Boca Raton), 115–136
Piper, P. J. 1984. Formation and actions of leukotrienes. *Physiol. Rev.*, **64**, 744–761
Rocklin, R. E., Bendtzen, K. & Greineder, D. 1980. Mediators of immunity: Lymphokines and monokines. *Adv. Immunol.*, **29**, 55–136
Slausen, D. O. & Finn, J. P. 1972. Meningo-encephalitis and panophthalmitis in feline infectious peritonitis. *J. Am. Vet. Med. Assoc.*, **160**, 729–734
Stewart, W. E. 1981. *The interferon system.* (Springer Verlag, Wien), 115–116
Stitt, J. T. 1986. Prostaglandin E as the neural mediator of the febrile response. *Yale J. Bio. Med.*, **59**, 137–149
Stringfellow, D. A. & Brideau, R. 1984. Interferons and prostaglandins. In: J. Vilcek and E. De Mayer (eds). *Interferon 2: Interferons and the immune system.* (Elsevier Press, Amsterdam), 147–163
Weiss, R. C. & Scott, F. W. 1981a. Pathogenesis of feline infectious peritonitis: Nature and development of viremia. *Am. J. Vet. Res.*, **42**, 382–390
Weiss, R. C. & Scott, F. W. 1981b. Pathogenesis of feline infectious peritonitis: Pathologic changes and immunofluorescence. *Am. J. Vet. Res.*, **42**, 2036–2048
Weiss, R. C. & Scott, F. W. 1981c. Antibody-mediated enhancement of disease in feline infectious peritonitis: Comparisons with dengue hemorrhagic fever. *Comp. Immun. Microbiol. Infect. Dis.*, **4**, 175–189
Wolfe, L. G. & Griesemer, R. A. 1971. Feline infectious peritonitis. Review of gross and histopathologic lesions. *J. Am. Vet. Med. Assoc.*, **158**, 987–993
Wolfe, L. S. & Coceani, F. 1979. The role of prostaglandins in the central nervous system. *Ann. Rev. Physiol.*, **41**, 669–684

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