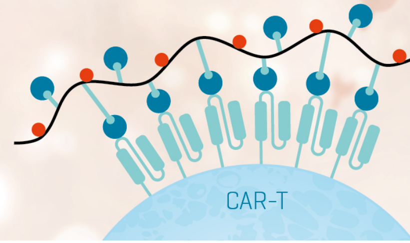
CAR-T Cell Quantification with Dextramer® Technology

Choose Your Target Antigen
We Make the Reagent for You

LEARN MORE



IMMUDEX®
PRECISION IMMUNE MONITORING

The Journal of Immunology

RESEARCH ARTICLE | DECEMBER 01 1980

Suppression by prostaglandin E1 of vascular permeability induced by vasoactive inflammatory mediators.

J C Fantone; ... et. al

J Immunol (1980) 125 (6): 2591–2596.
https://doi.org/10.4049/jimmunol.125.6.2591

Related Content

Effect of disodium cromoglycate on cutaneous basophil anaphylaxis.

J Immunol (September,1986)

The Effect of Locally Injected Vasoactive Amines on the Elicitation of Delayed-Type Hypersensitivity

J Immunol (January,1977)

An antigen-specific hypersensitivity which does not fit into traditional classification of hypersensitivity.

J Immunol (July,1989)

Downloaded from http://journals.aai.org/jimmunol/article-pdf/125/6/2591/1002217/2591.pdf by guest on 22 May 2025

0022-1767/80/1256-2591$02.00/0
THE JOURNAL OF IMMUNOLOGY
Copyright © 1980 by The Williams & Wilkins Co.
Vol. 125, No. 6, December 1980
Printed in U.S.A.

SUPPRESSION BY PROSTAGLANDIN E_1 OF VASCULAR PERMEABILITY INDUCED BY VASOACTIVE INFLAMMATORY MEDIATORS[1]

JOSEPH C. FANTONE,[2] STEVEN L. KUNKEL,[2] PETER A. WARD,[2] AND ROBERT B. ZURIER[3]

From the Departments of Pathology and Medicine (Division of Rheumatic Diseases), University of Connecticut Health Center, Farmington, Connecticut 06032

Systemic treatment of rats with prostaglandin E_1 or with its stable derivative, 15-(S)-15-methyl-Prostaglandin E_1, markedly reduce the increases in vasopermeability induced by the intradermal injection of histamine, serotonin, bradykinin, C3a, and compound 48/80. This inhibition is dependent on the dose of the vasopermeability factor and the duration of time between injection of the prostaglandin and intradermal injection of vasopermeability factor. The inhibition is associated ultrastructurally with a preservation of tight junctions between endothelial cells. The structure-function specificity of the inhibitory effects of the prostaglandin is shown by the diminished effects of prostaglandin A_2 and the lack of inhibition by prostaglandin $F_{2\alpha}$. These data provide evidence that PGE_1 interferes with the local effects of vasopermeability mediators and may explain the earlier observations that PGE_1 protects animals from immune complex-induced nephritis.

Since the earliest studies on inflammation, it has been observed that a characteristic series of events occurs in the course of an inflammatory reaction. This is especially true of the early vascular alterations that include changes in both vessel caliber and in blood flow, an increase in vascular permeability, and formation of a protein rich exudate (1, 2).

During the past two decades, many investigators have demonstrated the paramount role of changes in venules during the immediate phase of increased vascular permeability (3, 4). Ultrastructural studies suggest that increases in vascular permeability may result from contraction of juxtaposed venular endothelial or periendothelial cells. This results in a widening of intracellular junctions and allows extravasation of plasma proteins (5). Apart from direct endothelial damage such as that produced by physical injury, the most important inducers of vasopermeability changes appear to be vasoactive chemical mediators that initiate inflammatory reactions. These include histamine, serotonin, bradykinin, and the classical anaphylatoxins, all of which are released or generated during the early phases of acute inflammatory reactions caused by a variety of stimuli (6, 7).

Recent investigations have shown that the acute inflammatory reactions and subsequent tissue injury caused by tissue deposition of immune complexes can be suppressed by pretreatment of animals with both prostaglandin E_1 (PGE_1)[4] and a stable analog of PGE_1, 15-(S)-15-methyl PGE_1 (15-M-PGE_1) (8). The suppression of those reactions could be related to functional defects induced in circulating neutrophils, resulting in depressed chemotactic and phagocytic reactivity of the cells. In another system, it has also been shown that treatment of NZB/NZW mice with PGE_1 prolongs the survival time of these lupus-prone mice and diminishes the deposition of immune complexes in the kidney and the subsequent structural damage of renal glomeruli. The explanation for the effects of PGE_1 in these mice is not known.

It was therefore of interest to examine if systemic treatment of animals with prostaglandins influences the response to vasopermeability mediators. The mediators examined in this study included the direct acting mediators, histamine, serotonin, bradykinin, and the mast cell degranulating substances C3a and compound 48/80. Results of studies presented here indicate that treatment of rats with PGE_1 or its stable analog, 15-M-PGE_1, inhibits extravasation of soluble plasma constituents. These studies suggest that the anti-inflammatory activity of the PGE_1 compounds are, at least in part, due to their ability to prevent the effects of vasopermeability mediators.

MATERIALS AND METHODS

Animals. Adult male, Sprague-Dawley rats (Charles River Breeding Laboratories, Wilmington, MA) weighing approximately 250 g were employed.

Prostaglandin treatment. Prostaglandins were a gift of Dr. John E. Pike, Upjohn Company, Kalamazoo, MI. Stock solutions containing 10 mg/ml were prepared in ethanol and sterile saline and injected subcutaneously or given by mouth. The animals were then rested 1 to 48 hr before challenge with the vasoactive compound. For each data point in the following study, multiple skin sites were used on 3 to 5 animals.

Vasoactive mediators. Edema was induced by the intradermal (ID) injection of 0.1 ml of the following mediators: histamine dihydrochloride (neutralized), bradykinin, serotonin creatinine sulfate H_2O, and compound 48/80 (Sigma, St. Louis, MO). Various concentrations of C3a, prepared according to

Received for publication May 2, 1980.

Accepted for publication September 2, 1980.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

[1] This work was supported in part by National Institutes of Health Grants HL-23192, AI-09651, HL-07202, and AM-17309.

[2] Present address: Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan 48109.

[3] Present address: Division of Rheumatology, University of Pennsylvania Medical School, Philadelphia, Pennsylvania.

[4] Abbreviations used in this paper: PGE_1, prostaglandin E_1, 15-M-PGE_1, 15-(S)-15-methyl PGE_1; ID, intradermal.

Downloaded from http://journals.aai.org/jimmunol/article-pdf/125/6/2591/1002217/2591.pdf by guest on 22 May 2025

published procedures (9), were also examined as an immunologic mediator of vascular permeability.

Vascular responses. To assess the vascular responses to the various vasomediators and subsequent degree of prostaglandin suppression, 1 μCi of ^{125}I-rat serum albumin in phosphate-buffered saline (PBS) containing 2.5% Evans blue dye was administered i.v. before ID injections of the mediator. In selected cases, 1 ml (16 mg/ml) of colloidal carbon in PBS was given i.v. as an electron-dense marker to aid in ultrastructural visualization of the permeability changes. Negative control sites were injected ID with 0.1 ml of buffered saline and processed as described below. At various time points after challenge, animals were sacrificed and 1 ml of blood and 1 cm diameter skin sites were removed and measured for gamma emissions. A ratio of ^{125}I emissions per skin lesion/^{125}I emissions per 1 ml of blood served as the permeability index.

Vascular caliber and flow. Surface skin temperature was monitored before and at hourly intervals after prostaglandin administration with a telethermometer, BD-17 probe (Yellow Springs Instrument Co.) to assess changes in peripheral vascular blood flow.

Morphologic analysis. After assessment for radioactivity, portions from each skin site were fixed in buffered (pH 7.0) 10% formaldehyde for standard histologic staining. In selected cases, fresh tissue was fixed in glutaraldehyde (2%) and processed for transmission electron microscopy.

Statistical analysis. The Student's *t*-test or analysis of variance techniques was employed in comparing treated to non-treated animal groups.

RESULTS

Inhibition of permeability changes by 15-M-PGE$_1$. Pretreatment of animals with 200 μg of 15-M-PGE$_1$ (orally or subcutaneously) 6 hr before challenge produced significant inhibition of the permeability changes induced by a variety of vasoactive substances (Table I). In these animals, the vascular permeability induced by the direct acting mediators, bradykinin, histamine, serotonin, and by the mast cell degranulating substances C3a and compound 48/80 were inhibited from 70 to 93% (Table I). The low degree of permeability change in the saline-injected sites was also inhibited in the treated animals.

The effects of 15-M-PGE$_1$ treatment on vascular permeability induced by graded doses of histamine and bradykinin were examined by both radioactive marker and skin blueing. Figure 1 shows persistent reduction of the permeability change induced by both mediators, up to a concentration of 40 μg of the mediators. This reduction in permeability was also a consistent observation for serotonin, C3a, and compound 48/80 with the maximum concentration for each substance noted in Table I. By using a different parameter of vasopermeability, namely the diameter of skin blueing, comparable data on inhibition induced by 15-M-PGE$_1$ were noted. Inhibition of skin blueing by 15-M-PGE$_1$ paralleled inhibition of permeability increase as assayed by the permeability index. Typical skin blueing data with inhibition by 15-M-PGE$_1$ at several doses of histamine are seen in Table II. In each instance there was substantial reduction (60 to 69%) of the diameter of the blueing at each dose of histamine. The fact that the skin blueing technique is a less sensitive indicator of permeability change is reflected in the difference in statistical significance in comparing the skin blueing results with those obtained with the radiolabeled permeability marker.

The effect of pretreatment with 15-M-PGE$_1$ on the evolution of the permeability changes induced with histamine and compound 48/80 over a period of time was examined. Figure 2 shows significant inhibition of the permeability changes induced by both mediators up to 90 min after challenge. In each case, when the permeability changes approached their maximum, at 15 min after challenge, there was a greater than 80% reduction in the permeability index in the treated animals.

Time dependence of 15-M-PGE$_1$ administration on the in-

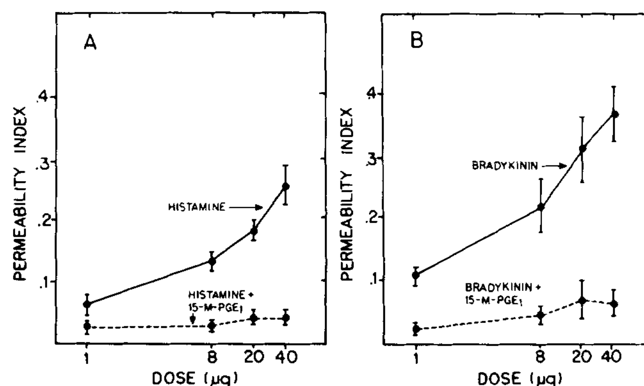


Figure 1. Dose response of vascular permeability changes induced by histamine and bradykinin, with suppression by 15-M-PGE$_1$. 15-M-PGE$_1$ was administered 6 hr before administration of the vasoactive mediator. Permeability index was determined as described in the *Materials and Methods* and represents a mean value of multiple skin sites on 3 to 5 animals. Vertical bars represent SEM.

TABLE I

Suppression of vasoactive mediator-induced vascular permeability

MEDIATOR	DOSE (ug)	MEAN PERMEABILITY INDEX		% INHIBITION	p VALUE
		CONTROL	TREATED		
HISTAMINE	40	.2602	.0404	84.5	< .005
BRADYKININ	40	.3750	.0682	81.9	< .005
SEROTONIN	20	.1428	.0433	69.7	< .01
C3a	10	.1549	.0303	80.5	< .01
48/80	40	.3827	.0255	93.3	< .01
SALINE	--	.0555	.0143	74.2	< .01

15-M-PGE$_1$ was administered 6 hr before challenge with vasoactive mediator. The exact permeability index was computed as described in *Materials and Methods*.

Downloaded from http://journals.aai.org/jimmunol/article-pdf/125/6/2591/1002217/2591.pdf by guest on 22 May 2025

TABLE II

Suppression of vasoactive mediator-induced skin blueing

HISTAMINE DOSE (ug)	MEAN BLUING DIAMETER (mm)		% INHIBITION	p VALUE
	CONTROL	TREATED		
40	13.5	4.9	63.7	<.001
20	11.3	4.0	64.6	<.03
8	9.3	2.9	68.8	<.001
1	5.2	2.0	61.5	<.05
0	3.0	2.0	33.3	<.05

15-M-PGE_1 was administered 6 hr before challenge with histamine. Mean blueing diameter was determined from multiple skin sites on 3 to 5 rats.

Downloaded from http://journals.aai.org/jimmunol/article-pdf/125/6/2591/1002217/2591.pdf by guest on 22 May 2025

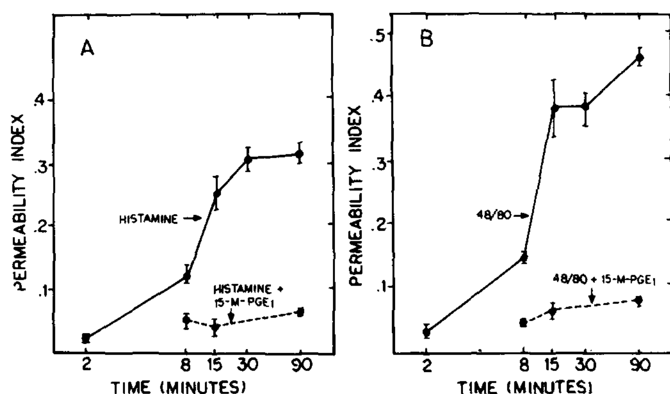


Figure 2. Time dependency of vascular permeability changes induced by 40 μg histamine and 40 μg compound 48/80 with suppression by 15-M-PGE_1. The method of administration of 15-M-PGE_1 and the permeability index are described in Figure 1. Vertical bars represent SEM. There was no statistical difference in the vascular permeability at 2 min after local administration of histamine or 48/80 between normal nontreated animals and animals treated systemically with 15-M-PGE_1.

TABLE III

Time dependence of 15-M-PGE_1 suppression of histamine-induced vascular permeability

TIME	PERMEABILITY INDEX	% INHIBITION	p VALUE
0	.2602	-	-
15 min	.0216	91.6	<.001
60 min	.0209	92.0	<.001
6 hrs	.0404	84.5	<.005
29 hrs	.0814	69.7	<.005
48 hrs	.1980	23.9	<.015

At various time points post-15-M-PGE_1 administration, animals were challenged with histamine, rested 15 min, and sacrificed. Permeability index was then computed as in the *Materials and Methods*.

hibition of permeability change. The subcutaneous administration of 15-M-PGE_1 resulted in a relatively rapid and long-lasting inhibition of histamine-induced permeability changes (Table III). Injection of 200 μg 15-M-PGE_1 15 or 60 min before histamine challenge (40 μg) resulted in more than 90% reduction in the vascular permeability index. Histamine challenge at 6 and 29 hr after 15-M-PGE_1 administration also resulted in significant reduction (84 and 69%, respectively) in the permeability index. Only after 48 hr was the effect of the 15-M-PGE_1 noted to be significantly attenuated (23% reduction in the permeability index). Inhibition of permeability induced by other mediators (serotonin, bradykinin, C3a and compound 48/80) followed a similar temporal pattern (data not shown).

Specificity of permeability inhibition by PGE compounds. The ability to modulate the histamine-induced increase in vascular permeability by using prostaglandin $F_{2\alpha}$ and prostaglandin A_2 was assessed and compared to the inhibitory effect of the PGE_1 compounds (Table IV). After subcutaneous administration of 200 μg of each of these prostaglandins followed 6 hr later by histamine challenge (with the intradermal injection of 40 μg histamine), only the PGE_1 and 15-M-PGE_1 demonstrated a significant reduction in vascular permeability. Prostaglandin E_1 inhibited the vascular permeability by 52%, whereas 15-M-PGE_1 inhibited the response by greater than 84%. In addition, there was a greater variation among animals with respect to suppression induced by PGE_1 as compared with 15-M-PGE_1, as noted in the p values in Table IV. Comparable suppression of permeability resulting from treatment with PGE_1 or its stable analog was noted at shorter time intervals (when mediator challenge was less than 2 hr after injection of PGE_1 or 15-M-PGE_1 or where doses of PGE_1 were used that were 2.5 times those of 15-M-PGE_1). Also at the shorter time periods, PGE_2 was as effective as PGE_1 in decreasing the vascular permeability induced by vasoactive mediators.

In contrast, despite its reported vasoconstrictor properties (10), $PGF_{2\alpha}$ did not prevent histamine-induced permeability. Prostaglandin A_2, a compound with vasodilator properties similar to PGE_1 and PGE_2 (11), showed a slight decrease in the permeability index, which was not statistically significant. These observations were consistent when other permeability mediators were used and suggest a specificity for the vasoprotective effect of PGE.

Ultrastructure of venules. The integrity of the dermal vessel walls was examined by transmission electron microscopy in both the prostaglandin-treated and nontreated animals. Figure 3 (*a-d*) represents the microscopic changes observed in the dermal venules in rats injected i.v. with colloidal carbon immediately before intradermal injection with the vasoactive mediator. Figures 3*b* and 3*d* show characteristic ultrastructural changes from nontreated animals in which there is separation of the endothelial cells with loss of tight junctions and formation

TABLE IV

Effects of various prostaglandins on histamine-induced vascular permeability

	MEAN PERMEABILITY INDEX	% INHIBITION	p VALUE
15-M-PGE_1	.0404	84.5	<.005
PGE_1	.1249	52.0	<.02
$PGF_{2\alpha}$	.2772	-6.5	N.S.
PGA_2	.2063	20.7	N.S.
CONTROL	.2602	-	-

Prostaglandins (200 μg/animal) were administered subcutaneously 6 hr before challenge. Mean permeability index was determined as described in the *Materials and Methods.*

of prominent endothelial gaps. Colloidal carbon is present in the gaps as well as in the subendothelial and extravascular spaces. In those animals treated with 15-M-PGE_1 (Figure 3*a* and 3*c*), endothelial cells appeared intact with the preservation of the tight junctions. The colloidal carbon was found only in endothelial vesicles and in very small amounts in the subendothelial areas. The integrity of the venule endothelial cells from PGE_1-treated animals was maintained after challenge with each of the vasoactive mediators.

DISCUSSION

The ability of prostaglandins to modulate both acute and chronic inflammatory responses has been well documented (8, 12). Prostaglandin E_1 and its derivatives have been shown to inhibit the reversed passive Arthus reaction in the skin (8) as well as adjuvant arthritis in rats (13). In both instances the inflammatory response was attenuated and the extent of tissue damage was reduced. The current study represents an attempt to examine the effects of PGE_1 and its 15-methyl derivative on the initial permeability changes in the skin that are mediated by both humoral and cell-derived vasoactive mediators.

The data presented above clearly show the ability of systemically administered PGE_1 and its 15-methyl analog to inhibit the vasopermeability changes induced by a variety of vasoactive mediators (histamine, serotonin, bradykinin) and mast cell-degranulating substances (compound 48/80 and C3a). This inhibition of vascular permeability by systemic treatment of rats with PGE_1 compounds stands in stark contrast to the local effects of PGE_1. Local administration of PGE_1 has been shown to potentiate the leakage of plasma proteins induced by bradykinin in rat skin (14) and by bradykinin and histamine in the dog knee joint (15). Local administration of PGE_1 has also been shown to have vasodilator actions (16). Again, these studies may demonstrate the differences between the local and systemic administration of prostaglandins and the complexity of the inflammatory system.

The persistent action of PGE_1, when administered subcutaneously, with up to 52% inhibition of histamine induced vasopermeability at 6 hr is accentuated by the observation that the 15-M-PGE_1 showed inhibition even at 48 hr after its administration. A similar observation was noted in the inhibition of the reversed passive Arthus model by using PGE_1 and its 15-methyl analog (8). The prolonged effect of 15-M-PGE_1 is a result of the protective effect of the methylated 15 position, which markedly reduces the susceptibility of 15-M-PGE_1 to oxidation by 15-hydroxy-prostaglandin dehydrogenase (17). Because of the abundance *in vivo* of this dehydrogenase, relatively large doses of the classical 15-hydroxyl-prostaglandins are required to demonstrate comparable effects.

The structure-function relationship between the ability of various prostaglandins to inhibit the permeability changes induced with vasoactive mediators are demonstrated by the inability of PGA_2 (a vasodilator substance) and $PGF_{2\alpha}$ (a potent vasoconstrictor) to have any inhibitory effects.

Electron microscopy revealed that PGE_1 treatment preserved tight junctions of endothelial cells and prevented the endothelial cell gap formation that follows the injection of a vasopermeability mediator. These findings implicate the endothelial cell as an important target of PGE_1 action in the inflammatory response. However, the possibility that the endothelial cell alterations may be secondary to the actions of PGE_1 at other sites (e.g., platelets, pericytes, or basement membrane) cannot be excluded.

Since PGE_1 is a known hypotensive agent, the possibility that changes in vascular permeability were a result of poor perfusion was addressed by monitoring external skin temperature before and after PGE_1 treatment. There was no statistically significant alteration of skin temperature with PGE_1 treatment and in an individual rat the maximum variation in skin temperature was in a net increase of 0.5°C. These data plus the fact that animals were rested 6 to 48 hr before vasoactive mediator challenge suggest that neither hypotension nor an acute stress response is responsible for the observed results.

The findings presented in this paper may explain why PGE_1 treatment of NZB/NZW (lupus) mice prevents renal glomerular deposition of immune complexes in these animals (18). The events responsible for renal deposition of the complexes have not been precisely defined. Complex size and solubility, antigen-antibody ratio, and avidity of antibody for antigen are all important factors in deposition (19). In addition, local release of vasoactive amines and other mediators of inflammation, and increased vascular permeability may be required (20). Thus, deposition of immune complexes can be induced by injection of histamine or by the release of vasoactive amines, during systemic anaphylaxis, or after mast cell degranulation (21). Although not an absolute requirement, platelet aggregation may amplify local vascular permeability. Thus the ability of PGE treatment to reduce mediator release from basophiles and leukocytes (8, 22) and to reduce vascular permeability may prevent deposition of circulating immune complexes and subsequent tissue injury.

Although prostaglandins and additional arachidonic acid me-

Downloaded from http://journals.aai.org/jimmunol/article-pdf/125/6/2591/1002217/2591.pdf by guest on 22 May 2025

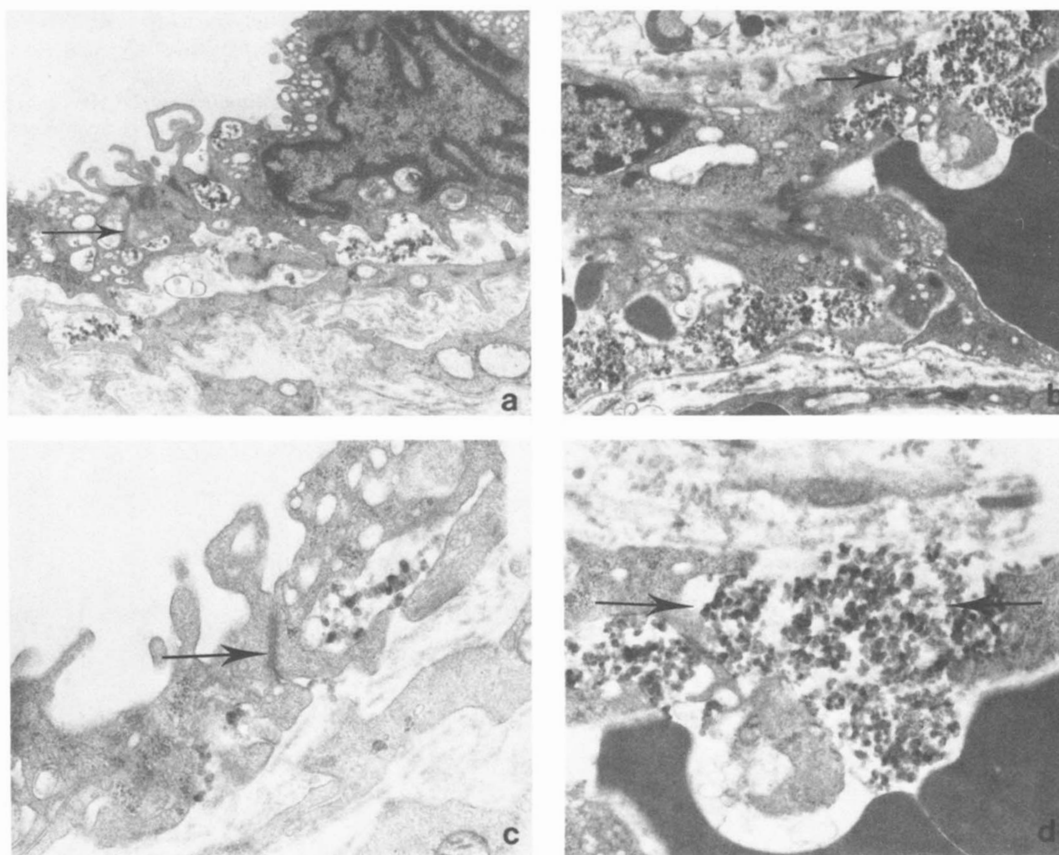


Figure 3. Effects of 15-M-PGE_1 on venule endothelium. Electron micrographs show venule endothelium 15 min after i.d. challenge with 40 μg of histamine in both nontreated rats (B.D.) and animals who received 200 μg of 15-M-PGE_1 (A.C.) 6 hr before histamine challenge. Sixteen milligrams of colloidal carbon was injected i.v. in each animal at the time of histamine challenge. Figure *A* (× 3,190) and *C* (× 10,260) show prominent pinocytotic vesicles with maintenance of endothelial tight junctions and no endothelial gap formation as a result of treatment with 15-M-PGE_1. The control animal, *B* (× 3,190) and *D* (× 10,260) show marked endothelial gap formation with loss of tight junctions. Arrows in *a*, *c* accentuate tight junctions; arrows in *b*, *d* accentuate gap formation.

tabolites have been clearly implicated in inflammation, their precise role remains to be clarified. The literature in the past has strongly implicated a proinflammatory role of many fatty acid derivatives (23). However, more recent reports (24) in conjunction with the evidence reported here demonstrate that prostaglandins of the E series have the ability to modulate inflammatory reactions and prevent tissue injury. As exemplified by the two preceding sentences the exact role of prostaglandins in inflammation remains complex; whether these compounds have use as therapeutic agents in modulating inflammation remains to be determined.

Acknowledgments. The authors would like to express their gratitude to Robin G. Kunkel for her electron microscopy expertise and to Barbara Hoekman for her secretarial support.

REFERENCES

1. Cotran, R. S., and G. Majno. 1964. A light and electron microscopic analysis of vascular injury. Ann. N.Y. Acad. Sci. 116:750.
2. Wilhelm, D. L. 1971. Increased vascular permeability in acute inflammation. Rev. Can. Biol. 30:153.
3. Hurley, J. V. 1972. Acute Inflammation. Williams and Wilkins Co., Baltimore. P. 33.
4. Spector, W. G., and D. A. Willoughby. 1968. The Pharmacology of Inflammation. English University Press Ltd., London. P. 11.
5. Majno, G., S. M. Shea, and M. Levanthal. 1969. Endothelial contraction induced by histamine-type mediators. J. Cell Biol. 42:647.
6. Maling, H. M., M. E. Webster, M. A. Williams, W. Saul, and W. Anderson. 1974. Inflammation induced by histamine, serotonin, bradykinin, and compound 48/80 in the rat: antagonists and mechanisms of action. J. Pharmacol. Exp. Ther. 191:300.
7. Wissler, J. H. 1972. Chemistry and biology of the anaphylatoxin related serum peptide system: purification, crystallization, and properties of classical anaphylatoxin from rat serum. Eur. J. Immunol. 2:73.
8. Kunkel, S. L., R. S. Thrall, R. G. Kunkel, J. R. McCormick, P. A. Ward, and R. B. Zurier. 1979. Suppression of immune complex vasculitis in rats by prostaglandin. J. Clin. Invest. 64:1525.
9. Hugli, T. E., E. H. Vallota, and H. J. Müller-Eberhard. 1975. Purification and partial characterization of human and porcine C3a anaphylatoxin. J. Biol. Chem. 250:1472.
10. Echt, M., O. H. Gauer, F. Kapteina, and L. Lange. 1972. Effects of prostaglandin E_2 and $F_{2\alpha}$ on cutaneous arteries and veins *in vivo* in the isolated rabbit ear. *In* Advances in the Biosciences, 9th International Conference on Prostaglandins. Edited by S. Bergstrom. Pergamon Press, Oxford. P. 353.
11. Horton, E. W. 1979. Prostanoids in health and disease. *In* Chemistry, Biochemistry, and Pharmacological Activity of Prostanoids. Edited by S. M. Roberts and F. Scheinmann. Pergamon Press, New York. P. 4.
12. Bonta, I. L., and M. J. Parnham. 1979. Chronic inflammatory conditions and mechanisms by which they may be modulated by prostaglandin-E. Eur. J. Rheum. Inflam. 2:97.
13. Zurier, R. B., and F. Quagliata. 1971. Effects of prostaglandin E_1 on adjuvant arthritis. Nature 234:304.
14. Thomas, G., and G. B. West. 1974. Prostaglandins, kinin and inflammation in the rat. Br. J. Pharmacol. 50:231.
15. Grennan, D. M., W. Mitchell, W. Miller, and I. J. Zeitlin. 1977. The

Downloaded from http://journals.aai.org/jimmunol/article-pdf/125/6/2591/1002217/2591.pdf by guest on 22 May 2025

effects of prostaglandin E_1, bradykinin and histamine on canine synovial vascular permeability. Br. J. Pharmacol. 60:251.
16. Thomas, G. 1980. Characteristics of prostaglandin E_1 potentiation of inflammatory activity of some agents. Prostaglandins 19:39.
17. Hansen, H. S. 1976. 15-hydroxyprostaglandin dehydrogenase: a review. Prostaglandins 12:647.
18. Zurier, R. B., I. Damjanov, D. M. Sayadoff, and N. F. Rothfield. 1977. Prostaglandin E_1 treatment of NZB/NZW F_1 hybrid mice. II. Prevention of glomerulonephritis. Arthritis Rheum. 20:1449.
19. Mannik, Mart. 1979. Characteristics of immune complexes and principles of immune complex disease. *In* Arthritis and Allied Conditions. Edited by D. J. McCarty. Lea and Febiger, Philadelphia. P. 256.
20. Kniker, W. T., and C. G. Cochrane. 1968. The localization of circulating immune complexes in experimental serum sickness. The role of vasoactive amines and hydrodynamic forces. J. Exp. Med. 127:119.
21. Cochrane, C. G. 1963. Studies on the localization of circulating antigen-antibody complexes and other micromolecules in vessels. J. Exp. Med. 118:503.
22. Lichtenstein, L. M., and R. DiBarnardo. 1971. The immediate allergic response: *in vitro* action of cyclic AMP and other drugs on the two stages of histamine release. J. Immunol. 107:1131.
23. Bonta, I. L., and M. J. Parnham. 1978. Prostaglandins and chronic inflammation. Pharmacol. 27:1611.
24. Kunkel, S. L., J. C. Fantone, P. A. Ward, and R. B. Zurier. 1980. Modulation of inflammatory reactions by prostaglandins. Prog. Lipid Res. In press.

Downloaded from http://journals.aai.org/jimmunol/article-pdf/125/6/2591/1002217/2591.pdf by guest on 22 May 2025