in other types of tumours (8)—that in the case of squamous cell epithelioma a connection may exist between the increase in suppressor cells and the formation of metastases. This hypothesis finds further support in the blastic response reduction to PHA and to ConA, as recorded by us in carcinoma patients with high peripheral blood levels of Tg.

The results of several studies indicate that, in addition to the suppressor cells, the lymphocyte T fraction with receptors for the Fc fragment of IgG comprises two cell populations, referred to respectively as K (responsible for antibody-dependent cellular cytotoxicity) and NK (to which cell-mediated spontaneous natural cytotoxicity may be attributed (10)). In the light of these data, the Tg lymphocyte increase demonstrated in the peripheral blood of patients with tumours may also be due to increased K and NK lymphocyte fractions. In this latter case, patients with squamous cell carcinoma of the skin would obviously exhibit high levels of lymphocytic cytotoxic activity (7). Furthermore, Tg lymphocytes are known to be less responsive to mitogens (5) and consequently their increased percentage may in fact be responsible for the reduced blastic response to PHA and to ConA, as demonstrated in our patients with high Tg blood levels.

The above immunopathogenetic considerations clearly indicate the need for further studies aimed at elucidating the biological role of T lymphocytes with receptors for the Fc fragment of IgG in patients with skin cancers.

ACKNOWLEDGEMENTS

This work was supported by Consiglio Nazionale delle Ricerche, Rome, Italy: Special Project "Control of Neoplastic Growth". We are grateful to Dr F. D'Ovidio for performing the statistics.

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Cutaneous Reactions to Two Fibrin-derived Peptides

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Received March 11, 1981

Abstract. Two previously isolated peptides (Ala-Arg-Pro-Ala-Lys and Ser-Gln-Leu-Gln-Lys-Val-Pro-Pro-Glu-Trp-Lys) derived from fibrinogen and cleaved off during plasmin-mediated fibrinolysis were investigated regarding their effect on vascular permeability in human skin. Intra-

dermal injection of the peptides produced wheals similar to those induced by bradkykinin. There was no flare around the wheal as seen after injection of histamine. The results indicate that fibrinogen-derived peptides may be of importance as permeability-increasing factors in inflammatory states.

Key words: Microvascular permeability; Fibrin-derived peptides; Intradermal injection

Formation of fibrin is a crucial event in the tissue reaction to trauma or to noxious agents of various kinds (7). During the propagation of the inflammatory process the fibrin is continuously degraded, the degradation products are removed, and new fibrin is formed (8). Fibrin degradation is a consequence of local conversion of plasminogen to plasmin, which occurs at a high rate in inflammatory lesions (10).

Two peptides which are split off from fibrinogen and fibrin early in the plasminolytic process have been shown to cause a local increase in microvascular permeability after injection in rat skin (1, 2). As it may reasonably be assumed that they are also formed in vivo and reach substantial concentrations in areas where fibrinolysis is pronounced (4), they are both strong candidates as contributors to the permeability increase that is part of the inflammatory reaction. In this study we investigated their effect on microvascular permeability in human skin.

MATERIALS AND METHODS

Eight healthy subjects and 5 patients with chronic urticaria were tested. None of them were taking antihistamine or anti-inflammatory drugs.

Tested material

The two fibrin-derived peptides, which since their purification have been named 6A (Ala-Arg-Pro-Ala-Lys) and 6D (Ser-Gln-Leu-Gln-Lys-Val-Pro-Pro-Glu-Trp-Lys), were synthesized by Drs. L.-E. Larsson, G. Lindeberg and U. Ragnarsson, Department of Biochemistry, Univerity of Uppsala, Sweden. Their origin in the fibrinogen molecule and their purification, isolation and subsequent synthesis have been described previously (1, 3). Doses from 6.25 to 50 nmoles in 0.05 ml saline were injected intradermally.

Bradykinin (BRS 640, Sandoz, 100 nmoles/ml) and histamine HCl 1:100000 (54 nmoles/ml) were used as reference substances. Saline injection were given for control purposes.

Testing procedure

Intradermal injections of 0.05 ml of the solutions were performed a random sites on the volar side of the forearm. The visible and palpable wheal was measured in two perpendicular directions 20 min later. In the event that erythema extended outside the wheal, its area was also measured.

Table I. *Wheal response after intracutaneous injection of peptide 6A, peptide 6D, bradykinin (Bk) and histamine (Hi) in human skin*

Mean wheal sizes ± S.D. are given

Substance	nmoles injected	Wheal (mm^2) $diameter_1 \times diameter_2$	Number of experiments/ number of volunteers
6A	50	84±35	(16/13)
6D	50	98±42	(9/9)
Bk	5	165±48	(14/13)
Hi	2.7	154±69	(9/7)

RESULTS

Both peptides 6A and 6D, as well as bradykinin and histamine, induced a wheal response after intracutaneous injection in human skin. After injection of histamine the wheal tended to be irregularly outlined, with a wide erythematous flare. In contrast, the wheal caused by injection of bradykinin and both fibrin derived peptides had a more even border with an erythematous rim which was always less than a few millimetres wide. The immediate reaction in patients with chronic urticaria was of the same magnitude as that in the healthy subjects.

The response was maximal after 20–30 min and the reaction subsequently faded at the same rate for all substances.

The amount of peptides 6A and 6D needed to increase microvascular permeability in human skin was more than 10–20 times that of bradykinin and histamine (Table I). On injection of various concentrations of peptide 6A there was a dose-related response (Fig. 1).

DISCUSSION

This investigation has shown that the two fibrin-derived peptides 6A and 6D increase microvascular permeability in human skin, thus extending the effect observed previously in a rat skin model to the human species. This result may be regarded as a necessary forerunner of further studies on the potential importance of these two or other similar peptides in various human pathological states.

Our results also confirm previous data indicating

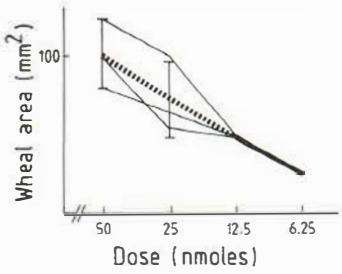

Fig. 1. Dose–response relationship after intracutaneous injection of peptide 6A. The abscissa represents the amount of peptide 6A, and the ordinate the wheal area expressed as the product of two perpendicular diameters. The individual curves for the three volunteers participating in this part of the study are all presented, as well as the mean ± S.D.

that local fibrinolysis is intimately linked to the development and perpetuation of the inflammatory process (9). Local fibrinolysis, i.e. the activity of locally formed plasmin, is very pronounced in the early phases of local tissue injury (7, 10). Plasmin increases microvascular permeability by several mechanisms, one of which might involve the formation of vasoactive fibrin-derived peptides (4, 9).

Since the surrounding flare seen after injection of histamine does not occur in response to either bradykinin or the peptides, it is less likely that their effect is due to any appreciable release of histamine. Furthermore, the lack of a delayed appearance of wheals as seen after injection of kallikrein (5) indicates that the kallikrein and peptide effects on microvascular permeability are different. The peptide effect is also different from the reaction with erythematous streaks and hyperalgesia seen after injection of prostaglandins (6).

Thus the mode of action of the two fibrin-derived peptides remains unknown. Further investigations on their mechanism of action and possible pathogenetic role in clinical cases seem warranted.

ACKNOWLEDGEMENTS

The help of L.-E. Larsson, Ph.D., G. Lindeberg, Ph.D. and Ulf Ragnarsson, Ph.D. in synthesizing the peptides and the excellent technical assistance of Rolf Wallin, B.Sc. and of Ms Inger Pihl-Lundin, are gratefully acknowledged.

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Subcorneal Pustular Dermatosis and IgA Gammopathy

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Received February 23, 1981

Abstract. An elderly male patient, who developed subcorneal pustular dermatosis 4 years after he first developed IgA gammopathy is described.

Key words: Subcorneal pustular dermatosis; IgA gammopathy

The pathogenesis of subcorneal pustular dermatosis remains unknown. The condition, first described in