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DECREASED CUTANEOUS REACTIONS TO KALLIKREIN IN PATIENTS WITH ATOPIC DERMATITIS AND PSORIASIS

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Abstract. Reactivity to intradermally injected kallikrein, histamine and bradykinin was studied in patients with various dermatoses. In patients with atopic dermatitis, reaction to kallikrein 5 to 24 hours after injection was strongly diminished. As a rule, these patients had no axon-reflex mediated flare after histamine and bradykinin; when the bradykinin induced weal disappeared, blanching was present at the site of the weal. In a group of patients with "healed" atopic dermatitis and normal levels of serum IgE, the reactions to kallikrein and histamine were normal. Patients with psoriasis had a lowered reactivity to kallikrein compared with that seen in healthy controls. The reactions to histamine and bradykinin were about the same as in the control group. The cause of the diminished reactivity to kallikrein is discussed. It may be associated with the low incidence of eczema and a diminished tendency to develop delayed hypersensitivity reactions observed in patients with psoriasis. A few patients with acne vulgaris also showed small reactions to kallikrein, but usually the reactions were within normal limits. Patients with eczematous dermatitis and a group of patients with various skin disorders also showed normal reactions.

Increased vascular reactions to kallikrein were found in patients with chronic urticaria (9). Preliminary results indicated a lowered reactivity in patients with atopic dermatitis and psoriasis and, occasionally, also in patients with acne vulgaris. The cutaneous reactions to kallikrein were therefore studied further in these and other dermatoses.

MATERIAL AND METHODS

Patients

Atopic dermatitis. (*a*) Twenty patients (8 men, 12 women), most of them between 18 and 30 years of age, with typical atopic skin changes which had usually been present for a long time. The skin was usually dry and slightly lichenified on the volar surfaces of the forearms. Raised levels of IgE (840 to 31,000 ng/ml) were present in ten of the patients, while six patients had levels within normal limits. Three patients had eosiniphilia, 9 to 18%; in one of them the IgE level was normal.

(*b*) Six patients (2 men, 4 women) between the ages of 15 and 30 years. They had previously suffered from atopic dermatitis, but were now free from dermatitic changes. Their IgE levels were normal.

Psoriasis. Forty-four patients (27 men, 17 women) with psoriasis of varying severity and duration. Fourteen of the patients were younger than 30 years of age. The areas used for tests were free from psoriatic lesions.

Acne vulgaris. Forty-two patients (16 men, 26 women) between 14 and 22 years of age. The acne was classified as Grade I to II in twenty-seven patients according to the criteria used by Pillsbury et al. (13); the remainder had Grade III to IV.

Eczematous dermatitis. Thirty patients (17 men, 13 women), twenty-six of whom were older than 30 years of age. They had eczematous dermatitis of varying severity, but the areas used for intradermal tests were free from dermatitic changes. Four of the patients had a hypostatic eczema, four had a nummular eczema, four had an allergic contact eczema, and the cause was unknown in the remainder. Positive patch test reactions were present in thirteen patients.

Various skin disorders. This group comprised thirty-one patients (8 men, 23 women), all of them older than 30 years of age and eight of them older than 60 years. Some of the diagnoses were: pemphigus vulgaris (1), purpura (1), rosacea (6), erythema nodosum (3), discoid lupus erythematousus (5), pruritus (2) hypertrichosis (1), mycosis fungoides (1), varicose leg ulcer (5), dermatitis herpetiformis (1).

Controls. Forty-five apparently healthy subjects (28 men, 17 women), mostly hospital personnel between the ages of 22 and 56 years. Twenty-five of these forty-five subjects had also been used as controls in a previous study (9), and twenty subjects were added subsequently. Two of the controls in the original group had suffered from acne and seborrhea between the ages of 13 and 17 years, but had not had active acne lesions in the most recent years.

Substances used for intradermal tests

Kallikrein (Padutin®, Bayer AG., Leverkusen, Germany). The dry powder containing kallikrein 40 U, thiomersal-

Table I. *Reaction to intradermal injection of kallikrein*

Diagnoses	No. of patients	Mean area of infiltration in mm² ± S.E.M. 0.3 h	1 h	2 h	5 h	24 h
Controls < 30 years	31	131±15	136±26	143±38	448±104	1109±140
Controls ⩾ 30 years	14	121±14	162±21	246±41	413±63	567±133
Atopic dermatitis < 30 years	20	145±22	117±23	131±26	106±27[c]	41±15[d]
Eczematous dermatitis > 30 years	30	145±11	201±19	254±31	470±47	422±74
Psoriasis < 30 years	14	122±16	201±45	192±33	196±76	191±84[d]
Psoriasis > 30 years	30	141±18	166±19	188±22	222±36[b]	225±85[a]
Acne vulgaris < 30 years	42	127±13	206±38	189±38	231±62	1094±126

p = probability that the difference between controls and others is caused by random factors.
[a] $p<0.05$. [b] $p<0.02$. [c] $p<0.01$. [d] $p<0.001$.

sodium 0.02 mg and sodium chloride 3.44 mg was dissolved in one milliliter of saline, giving a concentration of 40 U/ml. Histamine hydrochloride, 0.1 mg/ml. Synthetic bradykinin (BRS, bradykinin, Sandoz, kindly supplied by Sandoz, Stockholm, Sweden), 0.1 mg/ml.

Procedure

Injections of 4 U kallikrein, 0.01 mg histamine, and 0.01 mg bradykinin were given intradermally on the volar side of the forearm. The injected volume was 0.1 ml. The size of the reaction was measured 20 min and 1, 2, 5 and 24 hours after the injection and the area calculated as described previously (9).

RESULTS

In Table I the mean areas of the reactions to kallikrein are listed for the different groups of dermatoses as well as for two groups of controls.

Atopic dermatitis

(*a*) In the first two hours there were no significant changes in reactivity to kallikrein when compared with the controls, but at 5 and 24 hours the edematous infiltration was significantly smaller than that found in the control group. The erythema was usually slight or absent and the tenderness to pressure was also less pronounced than in other subjects.

The weals induced by histamine and bradykinin were not significantly smaller than in controls; however, the erythema was weak in most patients and the axon-reflex mediated flare was usually absent. When the weal was disappearing, the skin at the site of the bradykinin weal usually showed blanching 30 to 60 min after the injection. As a rule, there was also a blanching tendency after histamine.

(*b*) The reactions to kallikrein and histamine in six patients with a "healed" atopic dermatitis were normal (range of area of kallikrein infiltration at 24 hours: 835 to 1920 mm²).

Psoriasis

The reaction to kallikrein in patients with psoriasis was decreased at 5 to 24 hours, compared with healthy controls. In patients younger than 30 years, the decrease was best seen at 24 hours, which is the time for maximal reaction in healthy subjects of this age group. In the older patients the differences were most pronounced at 5 hours when the control subjects of this age group usually had their maximal reaction. The size of the reactions was not correlated to the severity or duration of the psoriasis. The weal and flare reactions to bradykinin and to histamine did not differ significantly from those of the control group.

Acne vulgaris

These patients showed wide variations in their sensitivity to kallikrein. Nine of the forty-two patients had remarkably small infiltrates (⩽100 mm²) or showed no infiltration either at 5 or 24 hours. Four of the nine patients with small reactions had a Grade III to IV acne, the others a Grade I to II. In most patients, however, the reactivity to kallikrein did not differ from that observed in controls, and the mean area of the kallikrein reaction for the whole group of acne patients did not differ significantly from that of the control group. As far as could be seen from this limited number of patients, the reactivity did not seem to be correlated to age, sex, severity of acne or to the ABO blood groups. The reactions to hista-

mine and bradykinin did not differ from those of the controls.

Eczematous dermatitis

The reactivity to kallikrein in this group of patients did not differ from that found in a control group. Also the reactions to histamine and bradykinin were the same as in the controls.

Various disorders

No obvious deviations from ordinary reactivity to kallikrein were observed in any of the patients included in this group.

Controls

In the control groups of the current study, the mean area of infiltration present 5 and 24 hours after the injection of kallikrein was somewhat larger than that found in the original control groups. In our earlier control groups, four subjects had minor reactions to kallikrein. Two of them had a moderate seborrhea and, between the ages of 13 and 17 years, they had suffered from acne. None of the controls who were added subsequently had a history of acne. They all had fairly large, but superficial and non-voluminous, reactions to kallikrein.

DISCUSSION

Atopic dermatitis

The presence of abnormal vascular reactions in atopic dermatitis is well known. They may be manifested as white dermographism, by delayed blanching after an intradermal injection of acetylcholine, by the absence of an axon-reflex mediated flare after an intradermal injection of histamine or by blanching after topical application of furfuryl-nicotinate. The blanching seems most likely to be due to vasoconstriction of the superficial vessels in the skin. A lowered threshold to epinephrine-induced blanching in patients with atopic dermatitis (8) and differences in the storage of catecholamines (18) might be possible mechanisms for the increased vasoconstriction, but the basic cause of this abnormal reactivity is unknown. An increased tendency to edema formation has also been claimed to be present in atopic skin and believed to cause or contribute to the blanching (2).

In the present study the reaction to local injection of kallikrein was markedly decreased compared with that seen in healthy subjects. Normally, an edematous infiltration of the skin is present 5 to 24 hours after the injection. In patients with atopic dermatitis this infiltration was usually insignificant. Intradermally injected bradykinin produced no or only a slight erythema and there was no axon-reflex mediated flare as seen in healthy controls of the same age. The initial reaction was usually followed by blanching after 30 to 60 min. The cause of these deviations from the normal response to kallikrein and bradykinin is not known, but it seems likely that it is connected with the tendency to vasoconstriction present in this disorder. A catecholamine release has been demonstrated in various experimental conditions after injection of both histamine and bradykinin (15). One possible explanation for the decreased reactions found in patients with atopic dermatitis might be that bradykinin and kallikrein induce a release of catecholamines which is more pronounced than in normal skin. The increased sensitivity to catecholamines found in the atopic skin may be a contributory factor. To some extent the kallikrein edema in these patients might also, in fact, be "hidden" in the dry or lichenified skin.

Nothing is yet known about the presence of IgE in atopic skin or the role of this immunoglobulin as a responsible factor for the vascular abnormalities of atopic dermatitis. It is known, however, that the serum levels of IgE tend to become normalized in patients with a "healed" atopic dermatitis (7). The six patients with a "healed" atopic dermatitis included in this study had normal levels of IgE and they also showed normal reactions to kallikrein and to histamine. The possibility might therefore be speculated upon that the presence of an increased amount of reaginic antibodies (IgE) may dispose to the abnormal vascular reactivity. The finding of abnormal vascular reactions in some patients with normal IgE would seem, however, to speak against such a possibility.

Psoriasis

One of the characteristics of psoriasis is the presence of tortuous, dilated and stretched capillaries (6, 17). They are best seen in the center of the plaques, but are, to some extent, also present in

non-involved skin (16). Whether the abnormal vessels are of primary significance for development of the condition or secondary to the psoriatic lesions is not known. The rate of the blood flow is increased in the psoriatic plaques (4). Little is known, however, about vascular reactions or about the response to vasoactive drugs in psoriatic skin. Holti observed a slight decrease in response to histamine and Trafuril® in the normal appearing skin both in psoriatic patients and their relatives (5), and Millberg found a delay in the development of reactive hyperemia (11).

In the present study, patients with psoriasis did not differ from healthy subjects in their reactivity to histamine and bradykinin, whereas the reactivity to kallikrein was markedly diminished. The mechanism of decreased reactivity to kallikrein in psoriasis is not known. Low levels of polypeptides and a blockade of dipeptidase activity in psoriatic skin have been reported by Paschoud et al. (12); this is a finding which might be connected with the presence of a reduction in kallikrein reactions in psoriasis. The possibility of an increased rate of blood flow also in the normal appearing skin, inducing a wash-away effect, might also be considered.

The diminished kallikrein reactions in psoriasis contrast with the highly increased reactions to this enzyme found in chronic urticaria (9). Clinically also these two conditions seem to be opposite to one another. Four patients out of a total of eight hundred and eighteen with psoriasis observed in the past two years also had a diagnosis of chronic urticaria, but the disorders were not active at the same time. Thus, during periods of urticaria, the psoriasis healed or improved markedly and, when their urticaria disappeared, the psoriasis returned.

There is also evidence that patients with psoriasis differ from healthy subjects in their immune response as well as in their ability to develop delayed inflammatory reactions (3). Eczematous reactions are not common in patients with psoriasis (1). Only five of the eight hundred and eighteen patients with psoriasis visiting this clinic in the past two years were found to have an eczematous dermatitis as well; three of these patients had a positive patch test. Patients with psoriasis are not easily sensitized with dinitrochlorobenzene (DNCB) and paranitrosodimethylaniline (NSMA) compared with normal subjects (3), and they have also been found to show a decreased immune response to plaque antigen (3). Epstein et al. therefore suggested that "psoriatic patients suffered a relative block in the immunologic system governing delayed hypersensitivity".

Since patients with abnormally increased sensitivity to kallikrein showed very strong delayed reactions to PPD tuberculin, it was previously suggested that the kallikrein-kinin system might be involved as mediator not only of urticaria formation, but also of delayed hypersensitivity reactions (10). In the current study the patients with eczematous dermatitis and a contact allergy had normal reactions to kallikrein. A diminished reactivity to kallikrein, together with a decreased tendency to develop delayed allergic reactions, found in psoriasis, may further strengthen the hypothesis that the kallikrein-kinin system might be of importance for these allergic reactions.

Acne vulgaris

In most patients with acne the reactions to kallikrein were within normal limits and the mean values did not differ significantly from those of a control group. However, among the forty-two patients with acne there were nine with definitely diminished reactions. Among the controls four subjects also had small-sized reactions. Two of them had acne and seborrhea in their adolescence. In view of the relationship claimed to exist between the vascular alterations in seborrheic conditions and psoriasis (14), it is interesting to find a lowered reactivity to kallikrein not only in psoriasis, but occasionally also in acne vulgaris.

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