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DETERMINATION OF FACTORS OF THE PLASMA KININ SYSTEM IN PLASMA SUBSTRATE SPECIMENS FROM PATIENTS WITH SPECIFIC, EXOGENOUS ALLERGIES

By

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In connection with the complex sequence of biochemical changes occurring in allergic states, kinins might, in addition to other active substances, appear in blood and contribute to the observed symptoms. Several authors have examined the possible relationship between anaphylaxis and kinin release (*Beraldo* 1950, *Lecomte* 1961, *Brocklehurst & Lahiri* 1962, *Back, Guth & Munson* 1963, *Back, Munson & Guth* 1963, *Diniz & Carvalho* 1963, *Dawson & West* 1965, *Cirstea, Suhăciu & Butculescu* 1965, *Scharnagel, Greeff, Lühr & Strobach* 1965, *Back, Wilkins & Steger* 1966, *Greeff, Scharnagel, Lühr & Strobach* 1966, *Ankier & Starr* 1967). In the present study of allergic subjects, the results of methods for determination of kininogen, kininase, prekallikrein, and rate of release of kinin (*Rinvik, Dyrud & Briseid* 1966, *Briseid, Dyrud & Rinvik* 1967, *Briseid, Dyrud & Arntzen* (in press), *Briseid, Arntzen & Dyrud* (in press) are reported. Plasma substrate specimens from eleven males and one female with specific, exogenous allergies were examined, using plasma specimens from healthy, presumably non-allergic, males for comparison.

METHODS

The methods used have been described previously: *plasma kininase* (Rinvik, Dyrud & Briseid 1966), *plasma kininogen* (Briseid, Dyrud & Rinvik 1967, Briseid, Dyrud & Arntzen in press), *rate of release of kinin* (Briseid, Dyrud & Rinvik 1967), *prekallikrein* (Briseid, Dyrud & Arntzen in press).

PATIENT MATERIAL

Selection. During the preliminary development of the methods, a co-incidental deviation from the normal pattern had been noticed in plasma from an individual who appeared to be "asthmatic" without further details.

The label "asthma" covers a variety of conditions, some of which seem to be caused by predominantly non-allergic factors. Even in cases showing signs of allergic etiology (such as positive family history, previous manifestations of an allergic nature, elevated circulating eosinophils, and symptomatic benefit from small doses of corticosteroids), considerable variations of the clinical syndrome occur, indicating that pathogenetic mechanisms may not be the same in each case. It is not unlikely that the different clinical types are related to the action of different chemical mediators, although it has been shown (Longbottom 1964) (Pepys 1959) that some of these clinical types are clearly related to a different type of antibody.

Among the various "allergic" syndromes with asthma as the presenting symptom, patients with "specific, exogenous allergy" of the immediate (or anaphylactoid) reaction type, constitute the best defined and most homogeneous group. The term indicates that their symptoms (asthma and/or allergic rhinopathy) are constantly released by contact with one or more defined substances containing the specific allergen.

Because of the non-debatable allergic origin of their symptoms, such cases were chosen for the present pilot study, in spite of the fact that histamine is known to be the dominant and all-important mediator substance in this type of case. Prophylactic antihistamine medication may even prevent the reactions. Little is known about the role of other mediator substances, such as serotonin, bradykinin, and slow reacting substance A (SRS-A).

It has been observed (Dyrud, Rinvik & Jensen 1965, Cline & Melmon 1966) that hydrocortisone may affect factors of the kinin system *in vitro*, and prednisone also in patients (Cline & Melmon 1966). Although plasma corticosteroid levels resulting from systemic corticosteroid therapy may not be sufficiently elevated to cause a change in our findings, patients who had received even minor doses of corticosteroids during the months prior to the collection of plasma samples were excluded from the study.

The predominantly male composition of the material was decided on, since the control cases, for reasons of convenience, were all males (case No. 1, the only female, was retained in the material since results in her case were well in accordance with the findings in the other patients).

TABLE 1
Survey of Case Material with Bronchial asthma.

Duration is given in Years. (y) Symbols: N = nose, E = eye, S = skin.
Skin reactions: + = mild, definite. ++ = moderate. +++ = marked (equals histamine control). ++++ = strong to maximal.
Upright arrow ($\uparrow$) = improvement.

Case No.	Age	Family dispos.	Asthma duration	Other manifest.	Cortico-steroids	Skin test	Eos./mm ³	Hyposens.
1	21	—	1½ y	NE 2 y	—	+++	730	+ $\uparrow$
2	57	—	5 y	ENS 25 y	—	+++	844	+ $\uparrow$
3	50	+	2 y	—	—	+++	?	+ $\uparrow$
4	18	+	3 y	N 13 y	—	++++	?	— (later $\uparrow$)
5	43	+	6+1 y	N 11 y	—	+	2250	— (elim. $\uparrow$)
6	23	(+)	20 y	S 3 y, N 13 y	prev.	+ $\uparrow$ +++	<300	+ $\uparrow$
7	31	(+)	7 y	—	—	+++	1900	+ $\uparrow$
8	22	(+)	10 y	S 22 y, N 17 y	prev.	+++	<300	+ $\uparrow$
9	27	+	1½ y	—	—	++++	594	+ $\uparrow$
10	28	?	1½ y	ENS 25 y	—	+++	?	+ $\uparrow$
11	19	+++	14 y	N 14 y, S 5 y	—	++++	719	+ $\uparrow$
12	26	—?	24 y	S 26 y	—	++++	<300	+ ($\uparrow$)

Some characteristics of the asthma cases are summarized in Table 1 (symbols are explained in the legend). In four cases allergic diseases occurred among close relatives, in three cases among more distant relatives, and in one case both parents are allergic.

Most cases have multiple urticarial reactions to intradermal testing. Only skin reactions related to allergens that gave bronchospasm when inhaled, are given in the table. Improvement following hyposensitization, indicated by an upright arrow, refers to clinical improvement as well as post-treatment failure to provoke bronchospasm by inhalation. (Brackets indicate partial relief). Case No. 5 was included with some doubt. He had asthma from age 1 to 7, and again during one year prior to examination. Initially wrongly diagnosed as emphysematic, after improvement, he had a vital capacity of 5600 ml, and his peak expiratory flow rate rose to about 600 l/min.

The few cases (No. 6 and 8) previously treated with corticosteroids had been taken off such drugs for four years or more.

The responses to specific hyposensitization correspond well with common experience in patients with asthma of reaginic type.

CONTROL MATERIAL

Selection. The donors of blood for plasma control specimens were not specifically screened in advance with regard to possible allergy. They were either staff members of the Institute of Pharmacy, or volunteers, claiming to be in good health at the time of the investigation. It was decided to use males only, in order to avoid any variation related to sex difference (menstruation, pregnancy); likewise, elderly people were not used for controls. Age distribution was 23 to 36 years (average 29) as compared to 18 to 57 years (average 30) for the patients.

At a later stage, following the elaboration of the results, it was questioned whether "healthy males" could be considered truly non-allergic. The ultimate nature of the genetic component in allergy is not yet known, but may well include inborn errors of metabolism that might affect enzymatic mechanisms. Considering the high incidence with which allergic diseases in one form or another occur in the general population, it is to be expected that a random sample might include people with previous allergies or who might be potentially allergic, demonstrated, for instance, by an allergic family predisposition.

In order to examine this possibility, each of the persons in the control group was asked to complete a rather detailed questionnaire with regard to occurrence of the following conditions: eczema, urticaria, allergic rhinitis, allergic conjunctivitis, asthma, chronic infection in nose or sinuses, or chronic or recurrent bronchitis. Any such case in the family should be stated, relationship specified, and in case of previous personal illness, information should be given about the year(s).

As might be expected, there were some positive responses, as shown in Table 2. It is, however, hard to explain why at least five, and probably six (case No. 5)

Grouping of clinical symptoms according to localization and type.

Pat.: Figure indicates age of occurrence.

Fam.: Parents, siblings, children; ++ means both father and mother.

Rel.: More distant relatives; ++ means father's and mother's side of family.

Control Case No.	Skin			Upper airways			Asthma			Chronic airway infection			Total		
	Pat.	Fam.	Rel.	Pat.	Fam.	Rel.	Pat.	Fam.	Rel.	Pat.	Fam.	Rel.	Pat.	Fam.	Rel.
1	24	+											1		1
2				2-12	+								1		1
3															
4							3-14	+		?					1
5			++		+				+	→7			1		2
6															
7															
8															
9				18	+								1		1
10		+			+				+					2	1
11										18→			1		
12									+						1
13															
14			+												1
Total	1	3	1	2	4		1	1	3	2			6	7	4

out of a total of 14 in our control group have had various forms of allergy, compared to an estimated 15-20 per cent incidence in the average European population. It has been suggested that choice of profession may be influenced by the total constitutional equipment behind an allergic syndrome.

Comments to individual cases in the control group:

Case No. 2. Mother hay fever, patient acute obstructive laryngitis repeatedly for a period of 10 years, allergic etiological factors probable, but debatable.

Case No. 4 was called in for clinical examination. He had a clear history of bronchial asthma that disappeared when he moved to another area 17 years ago, no symptoms at all since then, only daughter age 2, has had 6-7 attacks of asthma.

(It is probably incorrect to keep this case in the control group, but the figures were calculated before any knowledge of his history was obtained. In Table 5 the consequences of removing this case from the control group are shown by the figures in parentheses).

Case No. 5 reports allergic disease in both mother's and father's family: The mother's grandfather had eczema, the father's grandfather had asthma, the mother had hay fever, the father's sister had urticaria. The patient's recurring bronchitis before the age of 7 may well have been of partly allergic origin.

Case No. 6 is an only child, and returned a completely blank form.

Case No. 10 claims good personal health, his only sister has eczema and allergic conjunctivitis, his mother's brother had asthma.

RESULTS

Kininogen. Table 3 shows that the amounts present, of both the minor kininogen fraction and the total kininogen, were the same in the patients with allergic disease as in the healthy males.

Kininase. The plasma kininase determinations demonstrated in Table 4 revealed no significant difference between the activity levels in the plasma kininase preparations from the patients and from the normal material. The table shows that the results obtained were in close accordance with previously published data on the kininase activities in plasma specimens from 11 healthy men (*Rinvik, Dyrud & Briseid 1966*).

Rate of kinin release. Table 5 shows that the time periods corresponding to 66 per cent kinin release caused by hog pancreas kallikrein (Padutin®) were significantly shorter in the patients than in the healthy individuals, the average time periods required in the pathological substrate specimens being only about 50 per cent of the normal average values. When

TABLE 3

Determination of Total Kininogen and the Kininogen Fraction Released by Plasma Kallikrein in Plasma Substrate Specimens from:

- A. 13 healthy males; average values of data in press (*Briseid, Dyrud & Arntzen*).
 B. 12 patients with specific exogenous allergies.
 I. Total kininogen determined by the acetone activation method of *Briseid, Dyrud & Rinvik* (1967).
 II. The minor kininogen fraction determined by the kinin release caused by excess of plasma kallikrein preparation (*Briseid, Dyrud & Arntzen*, in press).

Subject number		Kinin released/ml plasma as μg bradykinin		II/I %
		I	II	
A	Mean	4.79	1.54	32.1
	s	0.32 (6.7 %)	0.22 (14.3 %)	4.2 (13.1 %)
B	1	6.0	1.7	28
	2	4.4	1.2	27
	3	5.0	1.5	30
	4	5.0	1.0	20
	5	4.6	1.7	37
	6	4.6	1.3	38
	7	4.0	1.4	35
	8	4.4	1.2	27
	9	3.9	1.4	36
	10	4.0	1.0	25
	11	4.3	1.4	33
	12	4.3	1.4	33
	Mean	4.54	1.35	29.9
	s	0.58 (12.8 %)	0.23 (17.0 %)	5.0 (16.7 %)

considering the data, however, it should be borne in mind that the 66 per cent release values were based on the maximum releases obtainable (after 60 minutes) with the same enzyme concentrations (*Briseid, Dyrud & Rinvik* 1967). Fig. 1 gives some additional information about the time-release relationship. The kinin release percentages shown in this figure refer to maximum release values obtained (after 60 minutes) with excess of enzyme, 4 units of padutin/ml plasma substrate. The figure clearly demonstrates that two facts contributed to the

TABLE 4

Determination of Plasma Kininase in Healthy Men and Men with Specific Exogenous Allergies.

Kininase determinations carried out according to the method of *Rinvik, Dyrud & Briseid* (1966).

- A. 10 healthy males; the enzyme preparations from subjects 1 to 7 and 11 to 13 (see Table 1) being pooled before assay and average value stated.
 B. 11 healthy males; average value of data previously published (*Rinvik, Dyrud & Briseid* 1966).
 C. 12 patients with allergies.

Subject number		ml plasma kininase preparation pr ml test solution causing 50 % bradykinin inactivation
A	Mean	0.187
B	Mean s	0.166 0.030 (18.1 %)
C	1	0.13
	2	0.13
	3	0.17
	4	0.16
	5	0.14
	6	0.16
	7	0.14
	8	0.14
	9	0.16
	10	0.19
	11	0.15
	12	0.18
	Mean s	0.154 0.019 (12.3 %)

considerable differences in rate of kinin release in the pathological and in the normal plasma substrate specimens demonstrated by the data in Table 5: an increased rate of release in the pathological specimens during the first part of the incubation period, and lower maximum release values after 60 minutes than observed in the normal substrate specimens. This was demonstrated for both padutin concentrations used.

Plasma prekallikrein. Table 5 shows the results of determinations of kininogenase activity obtained by acetone treatment of citrated plasma (*Briseid, Dyrud & Arntzen, in press*). The average kallikrein activity observed was higher for the pathological than for the normal plasma specimens when subject number 4 of the control material (see "Control Material") was omitted, 162 per cent of a standard preparation against 99 per cent. The individual variation between patients, however, was so large that the difference was just significant ($0.05 > P > 0.01$ by t-test).

DISCUSSION

The determinations of kininogen fractions and of kininase did not demonstrate any significant differences between plasma specimens from patients with allergic disease and from healthy men. The average prekallikrein level was higher in the patients, but the difference was barely significant. The rate of release of kinin, however, when estimated by the time needed at submaximal concentrations of padutin (hog pancreas kallikrein) for 66 per cent release of the maximum obtainable with the same doses, was considerably increased in the pathological substrate specimens. The time-release curves showed that this was partly due to a lower extent of release in the substrate specimens from the patients when concentrations of enzyme causing releases less than 100 per cent were employed, partly also to a higher initial release rate.

It is generally accepted that Padutin®, like other glandular kallikreins, acts directly on the kininogen to release kinin. According to *Jacobsen* (1966 a, b) glandular kallikreins released kinin from both kininogen fractions isolated by him, which are probably identical with the major and the minor kininogen fractions determined in the present study (*Briseid, Dyrud & Arntzen, in press*). Assuming a direct effect by padutin on the kininogen, the lower extent of release observed for submaximal enzyme concentrations in plasma substrate specimens from patients with specific, exogenous allergies than

TABLE 5

Subject number	I		II		
	Time in minutes corresponding to 66% kinin release caused by padutin, units/ml plasma		μ l kallikrein preparation /ml plasma substrate causing 50% kinin release		
	0.35	0.70	Test	Standard	Rel. activ. Test/Standard
A	1	21	30	30	1.0 (1.0)
	2		30	45	1.5 (1.5)
	3		80	50	0.6 (0.6)
	4*		15	40	2.7
	5	20	45	50	1.1 (1.1)
	6		20	30	1.5 (1.5)
	7		50	35	0.7 (0.7)
	8		45	45	1.0 (1.0)
	9	20	55	50	0.9 (0.9)
	10	—	40	50	1.3 (1.3)
	11	25	75	35	0.5 (0.5)
	12	18	40	30	0.8 (0.8)
	13	22	30	30	1.0 (1.0)
	Mean	21.3	42.7	40.0	1.12 (0.99)
B	s	—	19.2	8.7	0.57 (0.32)
	1	8	15	50	3.3
	2	—	25	45	1.8
	3	—	25	55	2.2
	4	12	30	60	2.0
	5	8	25	65	2.6
	6	12	95	50	0.5
	7	13	45	45	1.0
	8	15	20	35	1.8
	9	13	35	40	1.1
	10	11	60	40	0.7
	11	12	55	60	1.1
	12	13	40	50	1.3
	Mean	11.7	39.2	49.6	1.62
	s	2.2	22.3	9.2	0.82

* For information about subject number 4 of the control group, see "Control Material".

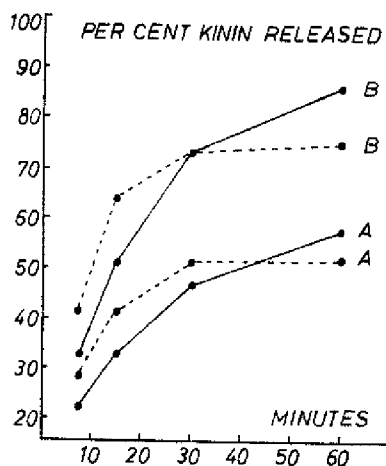


Fig. 1.

Rate of release of kinin in plasma substrate specimens from healthy men and patients with specific exogenous allergies.

Releasing enzyme: Hog pancreas kallikrein (padutin®).

Curves A: 0.35 units of padutin/ml plasma substrate.

Curves B: 0.70 units of padutin/ml plasma substrate.

————: Average release values based on substrate specimens from 13 healthy men.

-----: Average release values based on substrate specimens from 12 subjects with exogenous allergies.

Kinin released calculated as μg bradykinin/ml plasma and converted to per cent of kinin released by incubation with excess of enzyme (4 units padutin/ml plasma substrate) for 60 minutes at 37° .—For further details see text.

TABLE 5

Determination of Rate of Release of Kinin and Determination of Plasma Prekallikrein in Healthy Men (A) and Patients with Specific Exogenous Allergies (B).

- I. Rate of release of kinin caused by padutin® (hog pancreas kallikrein) according to the method of Briseid, Dyrud & Rinvik (1967).
 - II. Prekallikrein assay according to Briseid, Dyrud & Arntzen (in press).
- The individual kallikrein preparations were tested for kinin releasing activity in comparison with a standard kallikrein preparation. The same batch of plasma kininogen substrate was used in all tests.

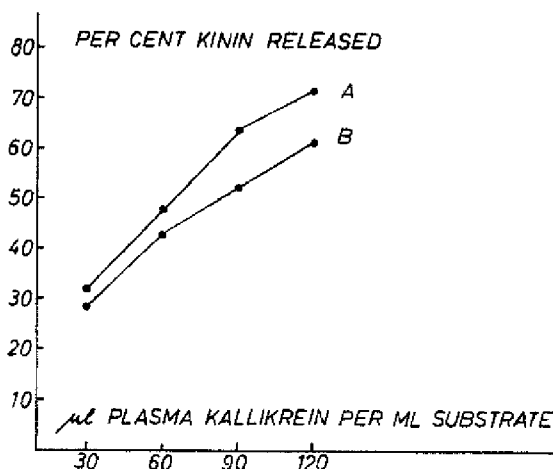


Fig. 2.

Extent of release of kinin in plasma substrate specimens from healthy men and patients with specific exogenous allergies.

Releasing enzyme: Plasma kallikrein prepared by acetone activation (*Briseid, Dyrud & Arntzen in press*).

A: Average release values based on substrate specimens from 13 healthy men.

B: Average release values based on substrate specimens from 12 subjects with exogenous allergies.

Kinin released calculated as μg bradykinin/ml plasma and converted to per cent of kinin released with excess of enzyme (1 ml plasma kallikrein preparation per ml substrate).—Incubation for 10 minutes at 37°.

in specimens from healthy individuals (Fig. 1) might suggest the presence of a higher level of kallikrein inhibitors in the patients. Abnormalities in the kininogen present might also be supposed to interfere with the extent of kinin release; the fact, however, that the average amounts of kinin released by *excess* of padutin were nearly the same for the normal and the pathological substrate specimens (Table 3) supports the view that differences in inhibitor levels must be the cause. In addition, no significant differences in relative amounts of the two kininogen fractions were observed in the two substrate materials (Table 3).

Experiments were carried out to examine if the differences

in extent of release, observed for the species-unspecific hog pancreas kallikrein in the normal and the pathological substrate specimens, were also present when human plasma kallikrein was used as releasing enzyme. The results shown in Fig. 2 demonstrate that this was in fact so. The extent of release of kinin as percentage of the maximum release obtained with excess of enzyme was higher in the substrate specimens from the healthy men than in the specimens from the men with allergic disorders throughout the enzyme concentrations range used. The time-release curves shown in Fig. 3 A demonstrate that the initially higher rate of release of kinin observed for padutin in the pathological substrate specimens (Fig. 1) was also detectable when plasma kallikrein was used as releasing enzyme. The difference was retained when the incubations were carried out in the presence of 12.5 per cent acetone, which both inhibited plasma kallikrein and eliminated the effect of inhibitors present (Fig. 3 B). Samples of the substrate specimens used for previous experiments were not available, and for the experiments demonstrated in Fig. 3 a batch of pathological substrate was used instead, based on specimens from 2 of the same patients and a batch of normal substrate based on specimens from 3 of the same healthy males. When these substrates were tested for kinin release caused by padutin, time-release curves similar to those shown in Fig. 1 were obtained.

When substrate specimens heated at 60° for 1 hour to destroy prekallikrein were used for time-release experiments with plasma kallikrein, the initially faster kinin release in the pathological substrate was eliminated, while the lower final extent of release in the same substrate, probably caused by kallikrein inhibitors, was unchanged (Fig. 3 C). A comparison of curves based on non-heated and heated substrates, however, demonstrated that a considerable destruction of inhibitors had taken place during heating at 60° , no halt in release being observed. Even if the higher rate of release in the pathological substrate could not be demonstrated after heating at 60° , other experiments indicated that the factor basically responsible for this increased rate of release must be relatively stable

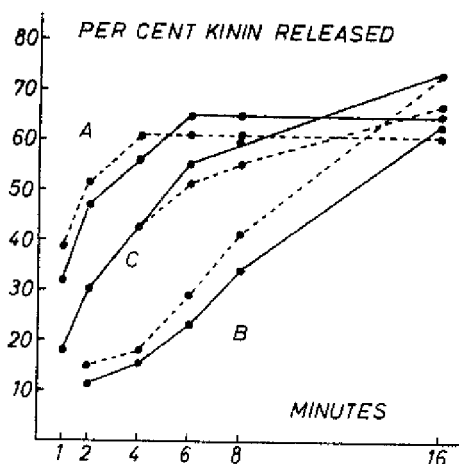


Fig. 3.

Rate of release of kinin in plasma substrate specimens from healthy men and patients with specific exogenous allergies.

Releasing enzyme: Plasma kallikrein (see Fig. 2), 50 μ l/ml substrate.

Curves A: No acetone present during incubation.

Curves B: 12.5 per cent (v/v) acetone present during incubation.

Curves C: Plasma substrate preheated at 60° for 1 hour. No acetone present during incubation.

————: Kinin release values based on a substrate specimen from 3 healthy men.

-----: Kinin release values based on a substrate specimen from 2 men with exogenous allergies.

Kinin released calculated as μ g bradykinin/ml plasma and converted to per cent of kinin released by incubation for 10 minutes at 37° with excess of enzyme (1 ml enzyme preparation/ml plasma substrate).—For further details see text.

at that temperature: Citrated plasma specimens from healthy males and from males with allergic diseases were exhausted of kininogen by incubation with acetone 16.6 per cent (v/v) for 17 hours; the acetone was evaporated under reduced pressure, the preparation was then heated at 60° for 1 hour and the kininase activity was subsequently eliminated as usual by addition of EDTA, 4 mg/ml citrated plasma. When each of these two preparations was added to normal plasma substrate, and two time-release curves were prepared by activation with

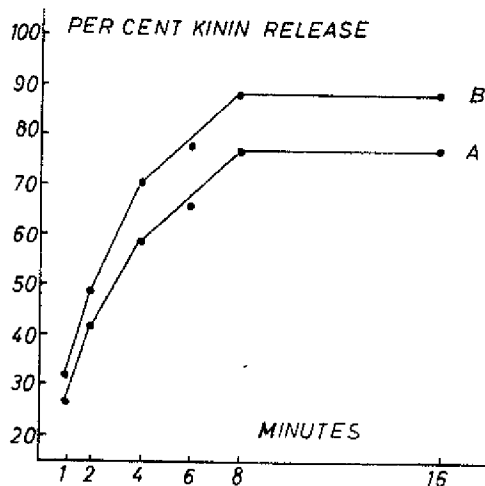


Fig. 4.

Rate of release of kinin in a normal plasma substrate.

The effects of addition of plasma substrates freed from kininogen, kininase, prekallikrein, and acetone susceptible kallikrein inhibitors, (modified plasma substrates).

Releasing enzyme: Plasma kallikrein (see Fig. 2).

Incubates: Plasma substrate, modified plasma substrate, and plasma kallikrein preparation (1 + 1 + 0.05 v/v).

A: Kinin release values based on a normal plasma substrate and a modified plasma substrate from 3 healthy men.

B: Kinin release values based on a normal plasma substrate from 3 healthy men and a modified plasma substrate from 2 men with exogenous allergies.

Kinin released calculated as μg bradykinin/ml plasma and converted to per cent of kinin released with excess of enzyme (1 ml plasma kallikrein preparations/ml normal plasma substrate).—Incubation for 10 minutes at 37° .—For further details see text.

plasma kallikrein, a difference in initial kinin release rate in both incubates was clearly demonstrable (Fig. 4).

The above experiments might suggest that an early factor in the kinin release system, which is fairly stable at 60° , is present in somewhat larger amounts, or can be more readily activated in plasma substrate from subjects with specific, exogenous allergies than in substrate from healthy individuals. Such an interpretation of the results was supported by observa-

tion of the spontaneous release obtained on dilution with saline in control experiments without addition of kinin-releasing enzyme, a definite tendency to higher release rate being observed in the pathological substrate. The results of such "blind" experiments might explain the fact that the initially higher kinin release rate was observed, not only for plasma kallikrein, but also for padutin, which is supposed not to be dependent on the kallikrein of the substrate for kinin release.

SUMMARY

Methods for *in vitro* estimation of parameters of the plasma kinin system were applied to patients with specific, exogenous allergies and to healthy males. Determinations of *kininogen fractions* and *kininase* activities did not reveal significant differences between the patients and the control material, but the average *prekallikrein* level was higher in the patients. The individual variation in the pathological material, however, being considerable, the established difference was barely significant ($0.05 > P > 0.01$ by t-test).

The *extent of kinin release* in plasma substrate specimens caused by submaximum concentrations of hog pancreas kallikrein (Padutin®) or plasma kallikrein, was lower in the patients than in the control group. The difference, probably caused by a higher level of kallikrein inhibitors in the patients, was not eliminated by preheating the substrate at 60° for 1 hour or by incubation in the presence of 12.5 per cent (v/v) acetone.

The *rate of kinin release* caused by the same enzymes was higher in the patients than in the control group. The difference was eliminated by preheating the substrate at 60° for 1 hour, but retained in the presence of 12.5 per cent (v/v) acetone.

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