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Kininase activity in the human placenta

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NON-SPECIFIC enzymes, called kininases, act on plasma kinins (met-kallidin, kallidin, bradykinin) and split off groups from these polypeptides thereby changing their activity or destroying it completely. A few kininases are present in the plasma: carboxypeptidases which inactivate plasma kinins by splitting off the C-terminal residue ("plasma kininase I"—"Carboxypeptidase N"—splits the Phe–Arg bonds) endopeptidase—"plasma kininase II" (cleaves the Pro–Phe sites of bradykinin), and aminopeptidases which attack the Met–Liz and Liz–Arg bonds of the *N*-terminal residue and thus convert met-kallidin and kallidin into bradykinin.[1] Since bradykinin is about from three to ten times (according to the ranges of concentration compared) more effective in measurements made on the isolated guinea-pig intestine than kallidin, the conversion process of kallidin into bradykinin can be detected in the isolated system as an increase in biological activity.[2] The red blood cells and other elements formed also contain kininases. Tissues are known to be sources of kinin destroying activity particularly the tissues of the kidney, lungs and liver. Further details on kinin-destroying processes are given in the literature.[2–5]

Our preliminary studies revealed a very high kinase activity in human placenta extracts.

Material and methods

The placenta extract was prepared as follows: a piece of human placenta was removed immediately after physiological labour, homogenized for 3 min in Tyrode solution at pH 7·3, 1 g of tissue to 2 ml solution and centrifuged at 1500 *g* × 15 min; the supernatant comprised the material tested. Determinations of the haemoglobin concentration in the supernatant indicated a blood contamination of about 1 per cent. A blood sample was taken from the antecubital vein of the same patient from whom the placenta was obtained, immediately after labour. The sample was mixed with 3·8% natrium citricum (1:10), half the sample was centrifuged (1500 *g* × 15 min) in order to obtain the plasma and the other half was frozen several times in order to release the haemolysate which was then centrifuged before use (1500 *g* × 15 min).

Kallidin and bradykinin from Sandoz S.A. were used as substrates for the kininase activity assays. One μg of kallidin or bradykinin dissolved in 1 ml of Tyrode solution was mixed with 0·5 ml of plasma, haemolysate or placenta extract and incubated for 5, 10, 30, 60 and 120 sec, after which the kinin activity of the mixture was determined on an isolated guinea-pig intestine. The degree of kinin inactivation was determined in comparison with the control, i.e. an intestine contraction induced by 1 μg of kallidin or bradykinin in 1·5 ml of Tyrode solution was taken to be 100 per cent.

Results, discussion and conclusions

During the first 10 sec of kallidin incubation with the placenta extract an increase in the pharmacological activity of the incubate of approximately 50 per cent of the control activity occurred after which the activity ceased within 3 min. In the bradykinin and placenta extract mixture only inactivation of that polypeptide was observed. After 10 sec the activity of the incubated bradykinin was found to be 50 per cent of that of the control, and after 60 sec incubation the bradykinin was practically completely inactivated. (Fig. 1).

In the experiments with kallidin two parallel processes were observed, one conversion of kallidin to bradykinin, the other, the inactivation of kallidin and bradykinin. Owing to the fact that the conversion of kallidin into bradykinin took place more rapidly than the parallel process of the kallidin and bradykinin inactivation,[3,6] a brief period of a rise in the pharmacological activity of the kallidin–placenta extract mixture was observed. This finding indicates that an enzyme with an activity similar to that of aminopeptidase is present in the placenta. It is not possible to establish on the basis of our findings what kind of enzymatic activity induces the kinin inactivation. Published data suggest that carboxypeptidases may be responsible for this inactivation.[4,5] Of the forty homogenates of placentae obtained after physiological labour, in two cases only a rapid disappearance of pharmacological activity was noted during the incubation of the placenta extract with kallidin. This may have been due to a considerably greater activity of the enzymes inactivating kallidin than that of the enzymes converting kallidin into bradykinin.

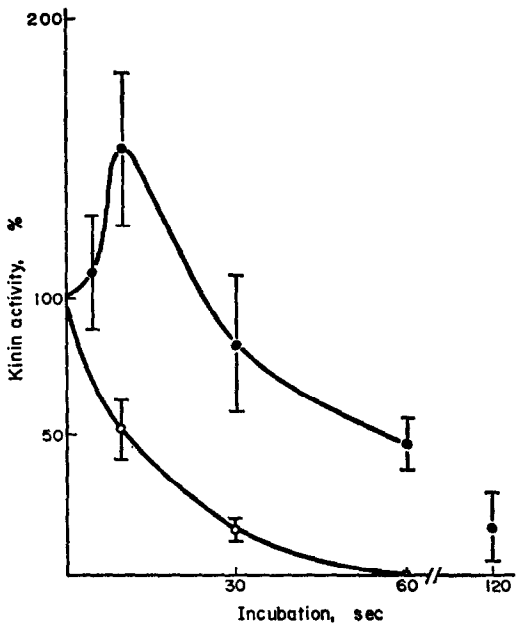

FIG. 1. Contractile activity of guinea-pig intestine induced by mixture of: kallidin and placenta extract (●); bradykinin and placenta extract (○) during incubation. The intestine contraction induced by control doses of kallidin or bradykinin alone was taken to be 100 per cent.

The kinin destroying activity of the human placenta is very potent, about ten times greater than that of blood haemolysate. It is difficult to explain the biological role of the kininase activity observed in the human placenta. It is possible that the placenta, a rich source of kininase, affects the kinins in the blood of both the mother and the foetus.

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