

Local bradykinin generation in hereditary angioedema

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Genetic deficiency of C1 inhibitor results in recurrent angioedema attacks consisting of localized swelling of the subcutaneous and mucous tissues. Ineffectiveness of histamine H₁ receptor antagonists in controlling these attacks excludes histamine as a mediator, whereas several lines of evidence indicate that the kinin family is involved. The possibility that bradykinin itself or a kinin-like peptide derived from the second component of complement is responsible for angioedema has been largely debated,^{1,2} and recently a predominant role of bradykinin in the process has begun to be accepted. In vitro, bradykinin has been shown to be responsible for the vast majority of the kinin-enhancing and permeability-enhancing activity that occurs in plasma deficient of C1 inhibitor.³ In vivo, we provided evidence that the bradykinin-releasing system (contact system) was activated during attacks of angioedema in C1 inhibitor-deficient patients.⁴

Recently we demonstrated substantially increased bradykinin concentrations in systemic plasma of patients during acute attacks of angioedema resulting from C1-inhibitor deficiency.⁵ Whether such an increase was the result of generation of bradykinin in the edematous area or a systemic activation of the kinin-releasing system could not be determined. One could hypothesize that angioedema attacks remain localized despite systemic C1-inhibitor deficiency either because the release of a vasoactive mediator is local or because increased local sensitivity exists (increased expression of receptors) for a mediator released systemically. If only local bradykinin generation is enhanced during attacks of angioedema, then even substantially increased systemic bradykinin levels should underscore the actual bradykinin generation at the site of angioedema.⁵ This study investigates whether bradykinin is generated locally by comparing

bradykinin plasma concentrations from the edematous area and an unaffected area within the same patients.

METHODS

In 2 patients with acute forearm angioedema resulting from hereditary C1-inhibitor deficiency, we measured bradykinin in blood samples taken simultaneously from the edematous area and from the contralateral unaffected forearm. Plasma bradykinin was measured specifically by radioimmunoassay after liquid-phase extraction and subsequent high-performance liquid chromatography as recently described in detail.⁵ The detection limit was 0.2 fmol/mL. Both intra-assay and interassay coefficients of variation were 18%.

RESULTS AND DISCUSSION

We found clearly increased concentrations of venous plasma bradykinin in the edematous forearm compared with the contralateral control arm (77 versus 9.5 fmol/mL and 46 versus 16 fmol/mL, respectively, with normal reference levels at 2.2 ± 2.2 fmol/mL) (Fig 1). Thus the increased levels of bradykinin in systemic circulation originated from 3-fold to 8-fold increased bradykinin concentrations in the blood draining from the affected arm. This finding strengthens our previous observation of enhanced bradykinin generation during angioedema attacks and clearly suggests that the event leading to bradykinin generation is local. Thus contact system activation products (high molecular weight kininogen cleavage products) that have been previously shown in the plasma of patients during angioedema attacks⁴ appear to be the consequence of such a local phenomenon and do not necessarily imply its systemic activation.

In conclusion, the present data confirm that the bradykinin levels measured in systemic circulation underestimate the actual bradykinin generation at the site of the angioedema: the blood draining from the edematous forearm is diluted in the venous pool of the right heart, and bradykinin is catabolized in the lung, where kininase II is particularly abundant. We also reinforce the hypothesis that angioedema attacks depend on the local activation of the kinin-releasing system by rarely identified triggers (physical trauma, oral surgery). Local symptoms seem rather specific of C1-inhibitor deficiency in which 1 or rarely 2 sites are involved at the same time.

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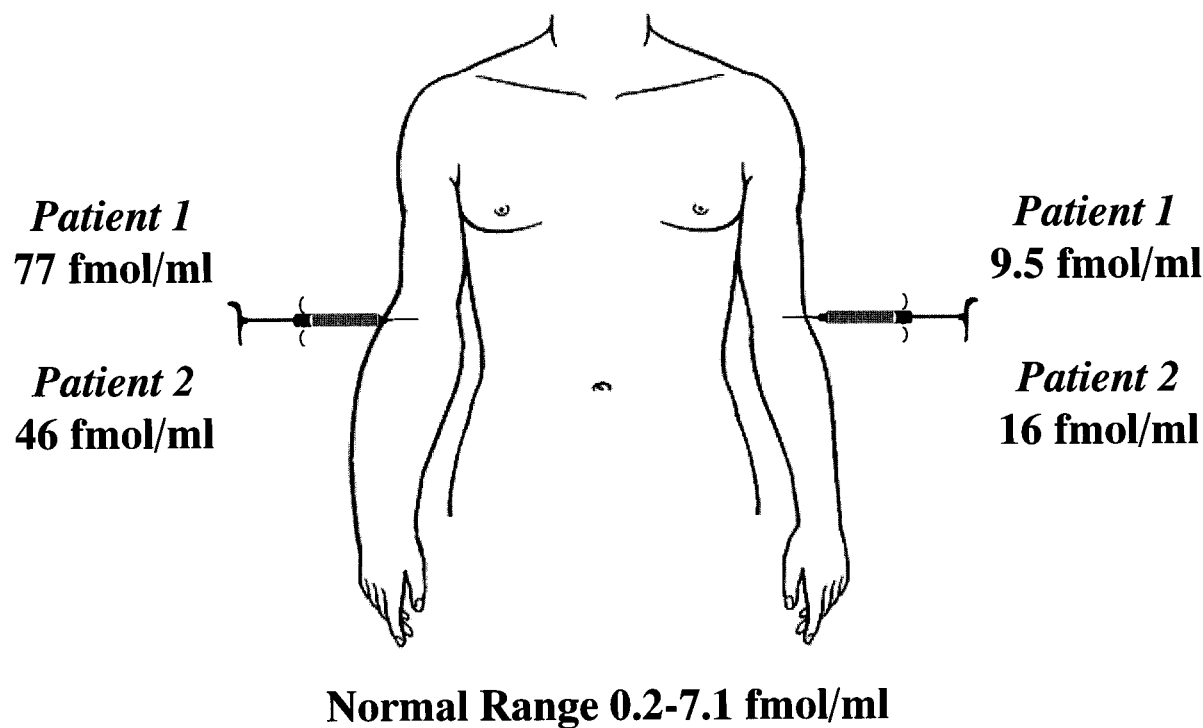


FIG 1. Bradykinin concentrations in 2 patients with hereditary deficiency of C1 inhibitor during an episode of brachial angioedema. Bradykinin plasma levels were increased in systemic circulation, but the blood draining from the affected arm had 8-fold and 3-fold higher levels than did the contralateral arm.

This situation is different from histamine-mediated phenomena that can be local (angioedema), multifocal (urticaria), or systemic (anaphylaxis). The efficacy of the lungs in inactivating bradykinin may minimize or prevent systemic effects of bradykinin.

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