

Allergy to Formaldehyde: Basophil Histamine-Release Test Is Useful for Diagnosis

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Established Facts

- Specific IgE measurement is useful as a test for patients who are allergic to formaldehyde, but the reliability of basophil histamine-release tests is not high.

Novel Insights

- Formaldehyde induced basophil histamine release only when it had been pretreated with albumin for days to weeks, suggesting that this molecule's slow interaction with proteins may affect the usefulness of this in vitro test.

Key Words

Basophils · Formaldehyde · Histamine release · IgE

Abstract

We describe a case of formaldehyde-induced urticaria with a positive test result for serum IgE antibody against this substance. Formaldehyde's slow protein-binding property may explain why basophil histamine-release tests using fresh formaldehyde solutions are not diagnostic, whereas the tests are useful if formaldehyde that had been stored with albumin is used.

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Introduction

Formaldehyde has long been recognized as both an allergen to sensitized subjects and an irritant to the general population [1]. Several reports have identified formaldehyde as a cause of anaphylaxis or urticaria based on the detection of specific IgE in serum [1, 2]; however, the reliability of skin tests is surprisingly low [3–5]. There was a recent report of successful induction of histamine release from a patient's basophils using formaldehyde-albumin conjugates purified by a dialysis elution procedure [6]. However, there have been no reports that sensitized patients' basophils are activated when in contact with di-

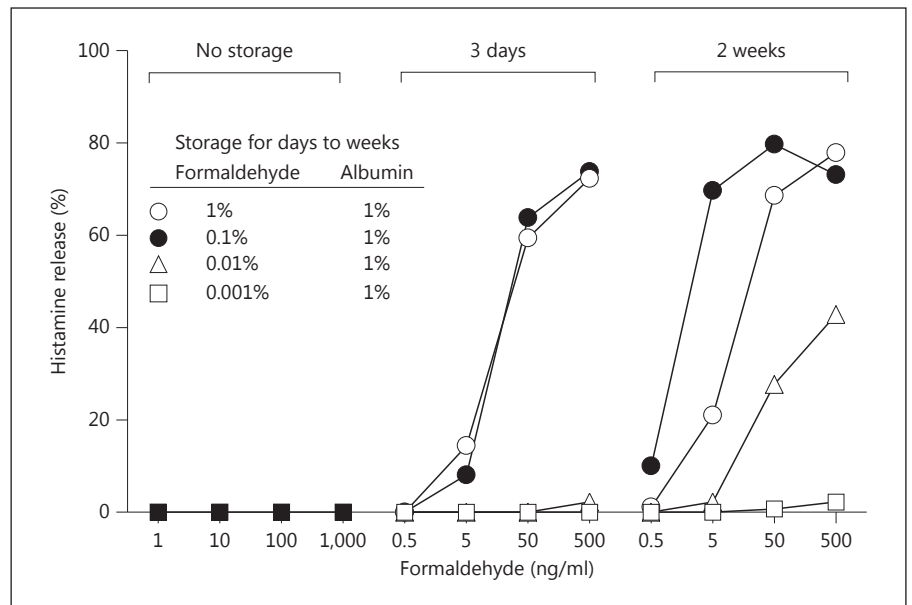


Fig. 1. Formaldehyde-induced histamine release from basophils after various durations of storage of formaldehyde mixed with albumin. Basophil preparations were prepared from the patient's blood or normal donor's blood followed by a passive sensitization procedure using the patient's serum [9]. Formaldehyde was diluted with PIPES buffer containing 0.03% human serum albumin and then mixed with the basophil preparations (left); formaldehyde at 0.001–1% was mixed with 1% human serum albumin, stored for 3 days

(middle) or 2 weeks (right) at 4°C and then diluted for cell-stimulation analyses. Basophils from 4 nonallergic donors never induced histamine release at the indicated formaldehyde concentrations (data not shown). Data shown are representative of three separate experiments, one with the patient's basophils and two using nonallergic donors' basophils that had been passively sensitized, all showing similar results, and are presented as the mean values of duplicate determinations.

luted formaldehyde. Here, we report a case of urticaria induced by paraformaldehyde used during root canal treatment. In vitro analyses indicated that our initial basophil histamine-release test using diluted formaldehyde was negative. We thus believed that there must be some underlying mechanisms that would explain the discrepancy between the basophil test results and the presence of serum formaldehyde-specific IgE.

Case Report

In the spring of 2013, a 28-year-old Japanese female was referred for dental therapy and evaluation of an allergic reaction following root canal treatment. One month earlier, she had developed generalized urticaria 1 h after application of a paraformaldehyde-containing root canal disinfectant (Periodon, Neo-Dental Chemical Products Co. Ltd., Tokyo, Japan). The urticaria resolved after taking an oral H₁ antihistamine. Before that allergic episode, she had undergone root canal treatment on several occasions, but never developed an allergic reaction. She had atopic eczema and her total serum IgE was elevated (1,770 IU/ml). Formaldehyde-specific IgE assessed by ImmunoCAP was strongly positive (>100 UA/ml), but serum-specific IgE to latex was negative. After obtaining informed consent, her venous blood was drawn, processed by dex-

tran sedimentation and utilized for basophil histamine release analysis [7]. Although her basophils showed no histamine-release reaction in response to diluted formalin or paraformaldehyde and she refused to undergo a skin prick test using formaldehyde, we concluded that paraformaldehyde, a source of formaldehyde, was the cause of her urticaria. Subsequently, she has strictly avoided contact with formalin-containing materials and has not experienced any similar allergic episodes.

We found that histamine release using formalin (Wako Pure Chemicals, Osaka, Japan) is not a sensitive test since extensive studies using various formaldehyde-mixed basophils failed to show degranulation (fig. 1, left). Next, we stored a mixture of 0.001–1% formaldehyde plus 1% human serum albumin (Japan Blood Products Organization, Tokyo, Japan) at 4°C. Following several days to weeks of storage, the solutions were serially diluted and tested for basophil stimulation without any dialysis step. The mixtures stored for 3 days (fig. 1, middle) and 2 weeks (fig. 1, right) showed basophil degranulating activity; the mixtures stored for ≥2 weeks were more potent inducers of histamine release, indicating that binding of formaldehyde to albumin is a slow process. Basophils from nonallergic subjects never responded to the formaldehyde-albumin conjugates, but these cells became responsive after undergoing a passive sensitization step using the patient's serum. As shown in figure 2, protein-unbound formaldehyde showed no effect on basophil activation since formaldehyde solution added at 300 or 1,000 ng/ml before stimulation with formaldehyde-albumin conjugates failed to enhance or suppress histamine release from basophils.

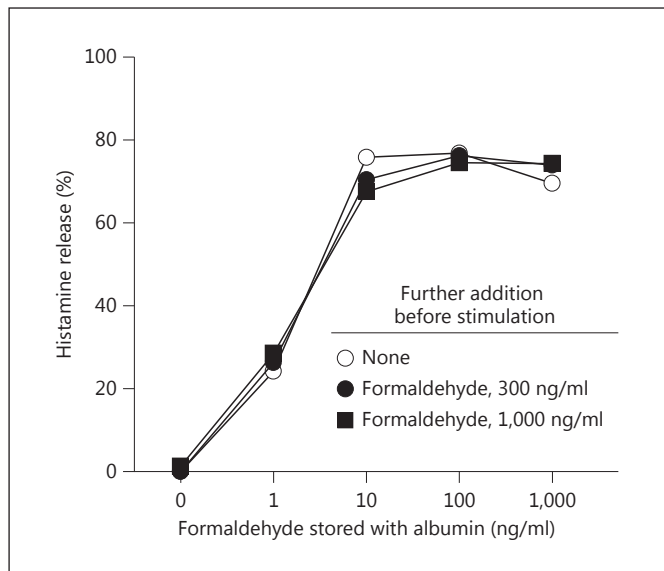


Fig. 2. Basophil histamine release was unchanged in the presence of protein-unbound formaldehyde. Basophils passively sensitized with the patient's serum were mixed with serially diluted formaldehyde (plotted on the x-axis), using 3-week-stored mixtures of 0.1% formaldehyde plus 1% albumin. Five minutes prior to cell stimulation, freshly diluted formaldehyde (unbound; final concentration 300 or 1,000 ng/ml) was added to albumin-conjugated formaldehyde preparations. Data shown are representative of two separate experiments showing similar results and are presented as the mean values of duplicate assays.

Discussion

We have clearly shown that histamine release from sensitive basophils occurs only when formaldehyde stored with albumin, but not freshly diluted formaldehyde, was used. A relatively higher concentration of

formaldehyde during storage is essential for the optimal activation of basophils, suggesting that either fully denatured albumin or albumin bound with abundant formaldehyde hapten can crosslink IgE on basophils more efficiently. We believe that the best conditions for allergen preparation in this system may be storage of albumin (1%) plus formaldehyde (0.1%) for 2 weeks or longer at 4°C; there is no need for dialysis. These results suggest that low levels of exposure to formalin will not reach the threshold of allergic manifestation even in highly sensitized subjects [8], which is consistent with the experience of our patient. On the other hand, locally administered, concentrated formaldehyde or paraformaldehyde that is not soon washed out may result in gradual formation of albumin that is heavily conjugated with formaldehyde, which may lead to allergic reactions in sensitized subjects. Repeated dental procedures involving local paraformaldehyde application probably accounted for our patient's sensitization to this substance and thus set the stage for her later allergic reaction.

Recently, molecular allergology has focused mainly on the precise determination of allergen molecules, usually by searching for allergens or epitopes in a crude mixture of proteins or other constituents. The results presented herein may expand the academic scope of molecular allergology. The chemical and/or biological properties of allergens, especially low-molecular-weight allergens, should also be further elucidated and taken into consideration in order to improve our understanding of the pathogenesis and pathophysiology of clinical allergy.

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