Stimulatory Effect of Histamine on Normal Human Melanocytes in Vitro

YASUSHI TOMITA, KAZUHISA MAEDA* and HACHIRO TAGAMI

Department of Dermatology, Tohoku University School of Medicine, Sendai 980

Histamine increased both the amount of tyrosinase and size of melanocytes even at concentrations as low as 0.1 μM (about 18 μg/ml) and at higher concentrations, these

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*Present address: Shiseido Laboratories, Yokohama 223, Japan.

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Normal human epidermal melanocytes became swollen and more dendritic and the immunoreactive tyrosinase increased markedly when they were cultured for 2 days with 5 μM of histamine. These results suggest that high dermal concentrations of histamine may be responsible for the induction of skin pigmentary changes associated with local proliferation of mast cells such as in urticaria pigmentosa and systemic mastocytosis. histamine; melanocyte; skin pigmentation; tyrosinase; urticaria pigmentosa

Melanocytes have a highly specialized function to make melanin pigment in the skin. Although hyperpigmentation is characteristic of skin lesions of urticaria pigmentosa in which mast cells proliferate massively in the dermis, its pathomechanism for hyperpigmentation has not been clarified yet. Mast cells are well known to release histamine by noxious and immunological stimuli and high concentrations of histamine were detected in the skin lesions of urticaria pigmentosa (Greaves and Sondergaard 1970; Granerus et al. 1983). Thus, it is reasonable to speculate that histamine may stimulate the melanocytes to induce hyperpigmentation in the skin lesions of urticaria pigmentosa. In this report we show for the first time that histamine has a direct stimulatory effect on normal human melanocytes in vitro.

Human melanocytes from the roof of suction blisters were cultured as described previously (Tomita et al. 1987). Immunofluorescent staining of cultured melanocytes was carried out using rat monoclonal antibody against tyrosinase and fluorescein isothiocyanate (FITC)-conjugated second antibody directed to the monoclonal antibody (TAGO Inc., Burlingame, CA, USA), and the intensity of fluorescence of FITC in each melanocyte was measured by a microphotometer (P-1, Nikon, Tokyo) according to the method described previously (Tomita et al. 1987). The cell perimeter, area as well as number of dendrites of each melanocyte were determined with an image scanner (PC-IN 502, NEC, Tokyo) connected to a microcomputer (PC-9801 VM, NEC, Tokyo) and appropriate soft ware as described previously (Tomita et al. 1987).

Histamine increased both the amount of tyrosinase and size of melanocytes even at concentrations as low as 0.1 μM (about 18 μg/ml) and at higher concentrations, these
changes became more apparent in a dose-dependent fashion. For example, as shown in Table 1, after 2-day culturing in 5 μM of histamine melanocytes that were immunohistochemically stained with the monoclonal antibody to tyrosinase showed a highly significant increase in fluorescence intensity. Histamine also changed the configuration of the melanocytes into more swollen and dendritic ones; there was an increase in the number of dendrites which appeared more slender and extended than those of the controls. These changes were already observed 6 hr after addition of histamine to the medium.

In the skin lesions of urticaria pigmentosa, high contents of histamine were reported; histamine was recovered even in the subcutaneous perfusates from the dermographic skin of patients in the concentrations ranging from 5 to 29.5 ng/ml (Greaves and Sondergaard 1970) and 25-590 μg of histamine/g of tissue was detected in the biopsy specimens from the skin lesions (Granerus et al. 1983). The present results therefore strongly suggest that a prolonged release of high concentrations of histamine from numerous mast cells might induce the hyperpigmentation in the lesions of urticaria pigmentosa and systemic mastocytosis.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of cells examined</th>
<th>Amount of immunoreactive tyrosinase (Relative fluorescent intensity)</th>
<th>Area (μm²)</th>
<th>Number of dendrites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>35</td>
<td>4.1 2.4</td>
<td>758 400</td>
<td>2.4 0.6</td>
</tr>
<tr>
<td>Histamine (5 μM)</td>
<td>41</td>
<td>13.8** 4.5</td>
<td>1994** 761</td>
<td>3.2†† 0.8</td>
</tr>
</tbody>
</table>

Melanocytes were cultured for 2 days MEM with 10% fetal bovine serum in the presence or absence of histamine.

**p < 0.01 against control values by Welch’s t-test.
††p < 0.01 against control values by Student’s t-test.

References