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HISTIDINE DECARBOXYLASE IN HUMAN BASOPHILIC LEUKEMIA (KU-812-F) CELLS

CHARACTERIZATION AND INDUCTION BY PHORBOL MYRISTATE ACETATE

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Abstract—The human leukemic cell line KU-812-F is known to differentiate into mature basophil-like cells under serum-free culture conditions. In the present study, the activity of histidine decarboxylase (HDC), a histamine-forming enzyme, in KU-812-F cells was found to be high, ranging from 10 to 57 pmol/min/mg protein. The great variation in HDC activity appeared to be due to different percentages and degrees of maturity of basophil-like cells during differentiation of this cell line. The enzyme was inhibited by α-fluoromethylhistidine but not by carbidopa, was unable to form dopamine from L-3,4-dihydroxyphenylalanine, and had a K_m value for histidine of 0.27 mM, indicating that it was HDC and not aromatic amino acid decarboxylase. The HDC activity increased 1.8-fold when the cells were stimulated by phorbol myristate acetate, which is known to activate protein kinase C, and this increase was blocked by staurosporine, a potent inhibitor of protein kinase C.

Recently, there has been much interest in L-histidine decarboxylase (HDC,§ L-histidine carboxylyase, EC 4.1.1.22), which decarboxylates histidine to form histamine, for the following reasons: (1) HDC is a useful marker of the histaminergic neuron system in the brain, (2) its inhibitor may be a drug for therapy of diseases involving histamine, and (3) HDC activity is induced in various conditions. However, most studies on HDC have been carried out in rodents [1–10], and little is known about HDC in human tissues [2, 3, 11], and particularly in leucocytes [12, 13], because of the difficulty in obtaining sufficient histamine-containing cells for study. KU-812-F cells, a human leukemic cell line established by Fukuda *et al.* [14], show immature basophilic characteristics under standard culture conditions. When stimulated with phorbol myristate acetate (PMA), KU-812-F cells develop into macrophage-like cells, whereas under serum-free culture conditions they differentiate into mature basophil-like cells. Thus, we used KU-812-F cells as a model of human basophils and measured their HDC activity. HDC activity has been reported to be increased by various stimuli [15–20], and Maeyama *et al.* [21] reported that HDC of rat basophilic leukemia (2H3) cells could be induced by PMA, oleoyl-acetylglycerol and cross-linked oligomers of IgE. In the present study, we characterized HDC in KU-812-F cells and examined whether its activity was increased by these reagents.

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§ Abbreviations: HDC, histidine decarboxylase; FMH, α-fluoromethylhistidine; PMA, phorbol myristate acetate; DOPA, 3,4-dihydroxyphenylalanine; AADC, aromatic amino acid decarboxylase; AB, alcian blue; and EGTA, ethyleneglycolbis(aminoethylether)tetra-acetate.

MATERIALS AND METHODS

Cells. KU-812-F cells were cultured under serum-free culture conditions in Hy-Medium 606 supplemented with 100 I.U./mL penicillin G and 100 μg/mL streptomycin [22]. Human histiocytic lymphoma (U-937) cells and human promyelocytic leukemia (HL-60) cells have been kept in our laboratory. Human eosinophilic leukemia (EoL-1) cells were provided by Dr. H. Saito of the Third Department of Internal Medicine of this medical school.

Cell morphology. In each experiment cytocentrifuged smears were prepared in a cytospin II (Shandon, U.K.) and stained with Wright-Giemsa stain or alcian blue (AB)-safranin stain. Cells were fixed with Carnoy's solution when AB was used [23].

Assays of enzyme activities. HDC was extracted from KU-812-F cells at 4°. KU-812-F cells were centrifuged at 140 *g* for 7 min, and the pellet was suspended in 0.5 mL of ice-cold HDC solution [0.1 M potassium phosphate buffer, pH 6.8, 0.2 mM dithiothreitol, 0.01 mM pyridoxal 5'-phosphate, 1% polyethylene glycol (average molecular weight, 300), 100 μg/mL phenylmethane sulfonylfluoride, and 0.1 mM EGTA]. Then the cells were sonicated for 20 sec in a sonicator (Tomy Seiko Co. Ltd., Tokyo, Japan) in an ice bath. The homogenate was centrifuged at 12,000 *g* for 20 min, and the supernatant fraction was dialyzed three times against 100 vol. of HDC solution. HDC activity was assayed fluorometrically as described previously [5, 24]. Briefly, the enzyme was incubated with 0.25 mM L-histidine,

unless otherwise stated, for 15 min to 6 hr at 37° in 1.0 mL of HDC solution, and the reaction was stopped by adding 0.04 mL of 9.2 M perchloric acid. In inhibition studies, HDC was preincubated with various concentrations of α-fluoromethylhistidine (FMH) or carbidopa for 30 min, and then aliquots of less than 1/100 volume of the mixtures were transferred to the assay mixture to measure remaining HDC activity. After a brief centrifugation, the supernatant fraction was subjected to HPLC to measure histamine [25]. The activity of aromatic amino acid decarboxylase (AADC, aromatic L-amino-acid carboxylyase, EC 4.1.1.28) was determined by an HPLC-electrochemical detection method as described by Nagatsu *et al.* [26] with L-DOPA as a substrate. For comparison, AADC was extracted from rat kidney as described by Ando-Yamamoto *et al.* [27]. Protein was measured by the method of Lowry *et al.* [28] with bovine serum albumin as a standard.

Treatment of cells with various reagents. KU-812-F cells were incubated with 0.1 to 100 nM PMA, or 0.05 to 1.0 μM calcium ionophore (A23187), and centrifuged at the indicated times. In experiments using anti-IgE, KU-812-F cells were first incubated with monoclonal human IgE for 30 min at 37°, and then, after washing with medium, with 100- to 1000-fold dilutions of anti-human IgE. Then HDC was extracted and assayed as described above. The effect of staurosporine was examined by pretreating the cells with 0.5 to 100 nM staurosporine for 10 min before stimulation.

Chemicals. PMA and calcium ionophore (A23187) were purchased from the Sigma Chemical Co. (St. Louis, MO, U.S.A.) and were dissolved in dimethyl sulfoxide. FMH was a gift from Dr. J. Kollonitsch of Merck Sharp & Dohme (Rahway, NJ, U.S.A.). Carbidopa was a gift from Dr. Y. Endo of the Department of Pharmacology, School of Dentistry, Tohoku University. Human monoclonal IgE was from Serotec Ltd. (Oxford, U.K.). Anti-human IgE and staurosporine were from ICN Immuno-Biologicals (Rehovot, Israel) and the Kyowa Hakko Co. (Tokyo, Japan) respectively. Other chemicals were analytical grade.

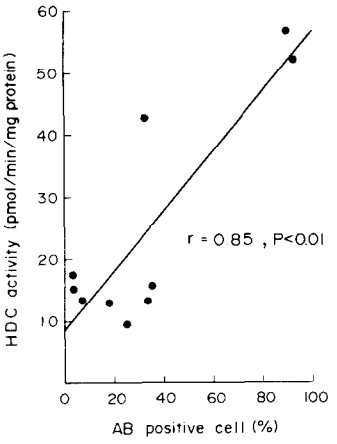

Fig. 1. Correlation of percentage of AB-positive cells and HDC activity in KU-812-F cell cultures. KU-812-F cells were cultured under serum-free conditions. Then the percentage of AB-positive cells was calculated after staining and the HDC activity was measured after extraction, as described in Materials and Methods. The correlation was significant ($r = 0.85$, $P < 0.01$).

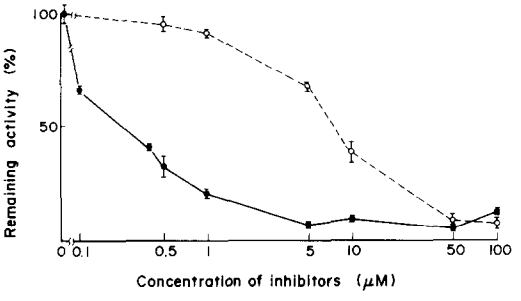

Fig. 2. Inactivation of HDC by FMH and carbidopa. Samples containing HDC activity were preincubated for 30 min with various concentrations of FMH (●) or carbidopa (○), and then the remaining HDC activity was assayed as described in Materials and Methods. Values are means ± SE (N = 3). The HDC activity in the absence of inhibitors was 12.3 ± 0.8 pmol/min/mg protein.

RESULTS

Presence of HDC activity in KU-812-F cells. In these experiments, the percentage of AB-positive cells in KU-812-F cultures under serum-free conditions ranged from 3 to 93%, and the HDC activity from 10 to 57 pmol/min/mg protein without stimulation; there was a clear correlation between the percentage of AB-positive cells and the HDC activity in KU-812-F cell cultures (Fig. 1; $r = 0.85$, $P < 0.01$). The HDC activity was proportional to the reaction time and enzyme concentration, and the K_m value of HDC for L-histidine was 0.27 mM (data not shown). In other human lymphoma and leukemia cell lines (U-937, HL-60, EoL-1), no HDC activity was detectable under our assay conditions either before or after stimulation with 50 nM PMA (data not shown).

Inactivation of HDC activity by FMH. Samples containing HDC activity were preincubated with various concentrations of FMH for 30 min at 37° in HDC solution without histidine, and then their remaining HDC activity was assayed after adding histidine. As shown in Fig. 2, FMH (1.0 μM) inhibited HDC concentration dependently and reduced HDC activity to about 21%; the IC_{50} was calculated as 0.2 μM. On the other hand, 1.0 μM carbidopa, which almost completely inhibited the AADC activity of rat kidney, did not inhibit HDC significantly, but at its higher concentrations it was inhibitory.

Effects of PMA, calcium ionophore, and anti-human IgE on HDC activity in KU-812-F cells. Figure 3A shows the increase in HDC activity after 4 hr as a function of the concentration of PMA. The change in HDC activity after addition of 50 nM PMA to cultures of KU-812-F cells is shown in Fig. 3B. The HDC activity increased within 1 hr after addition of PMA, reached a maximum in 4 hr (1.8-fold), and

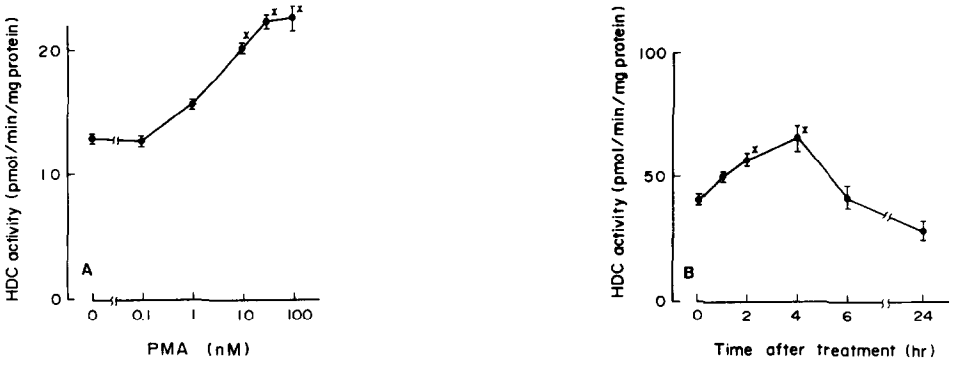

Fig. 3. Induction of HDC activity by PMA. (A) Typical concentration–response curve of the increase in HDC activity induced by PMA 4 hr after its application. (B) Typical time–course of increase in HDC activity after a single application of PMA (50 nM) to the culture. KU-812-F cells were treated with PMA, and the HDC activity was measured at the times indicated as described in Materials and Methods. The proportions of AB-positive cells in the experiments in (A) and (B) were 19.0 and 32.2% respectively. Values are means ± SE (N = 3). An asterisk (*) indicates a significant difference from control, $P < 0.05$.

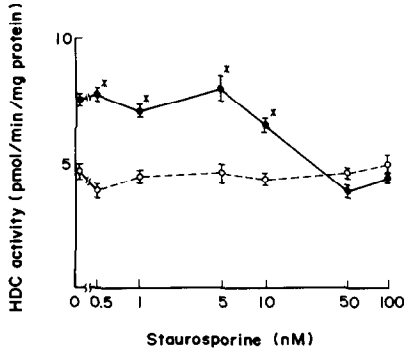

Fig. 4. Effect of staurosporine on HDC increase induced by PMA. KU-812-F cells were treated with 50 nM PMA in the presence of various concentrations of staurosporine. Closed and open circles represent values in the presence and absence of PMA respectively. Values are means ± SE (N = 3). An asterisk (*) indicates a significant difference from the values without PMA, $P < 0.05$. Cultures contained 20% of AB-positive cells.

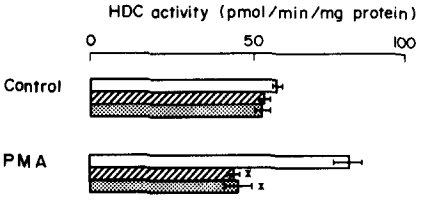

Fig. 5. Effect of cycloheximide on the increase in HDC activity induced by PMA. KU-812-F cells were treated with 50 nM PMA in the absence or presence of 5 or 20 μg/mL cycloheximide for 4 hr, and then HDC activity was measured as described in Materials and Methods. Cultures contained 89.8% AB-positive cells. Key: (□) no cycloheximide; (▨) 5 μg/mL cycloheximide; and (▩) 20 μg/mL cycloheximide. Values are means ± SE (N = 3). An asterisk (*) indicates a significant difference from the values without cycloheximide, $P < 0.05$.

returned to the unstimulated level after 24 hr. PMA did not change the morphology of the cells even after 24 hr. Neither calcium ionophore nor anti-human IgE caused an appreciable increase in HDC activity; HDC activities of control cells (untreated) and of cells treated with 0.5 μM calcium ionophore and 300-fold diluted anti-IgE were 12.0 ± 0.2, 10.5 ± 0.4 and 11.0 ± 0.5 pmol/min/mg protein respectively.

Effect of staurosporine on the HDC increase by PMA. To show further evidence for the involvement of protein kinase C in the increase of HDC activity induced by PMA, we examined the effect of staurosporine. As shown in Fig. 4, the increase was inhibited by staurosporine concentration dependently. Staurosporine did not affect the basal HDC activity without stimulation by PMA.

Effect of cycloheximide on the increase of HDC activity. The increase in HDC activity in response to PMA was abolished in the presence of 5 μg/mL of cycloheximide (Fig. 5).

DISCUSSION

In a search for human cells containing high HDC activity, we screened various normal and tumor cell lines. Human basophils contain histamine (1.9 to 3.1 pg/cell) [29], and HDC activity has been detected in leukocytes from normal persons and patients with hyperbasophilia [12], but this activity is lower than that in rodent tissues used for purification of HDC, such as fetal rat liver and mouse mastocytoma. We could not detect any measurable HDC activity in various human tumor cell lines, as described before, but detected higher HDC activity in KU-812-F cells, ranging from 10 to 57 pmol/min/mg protein, without stimulation. The reason for the wide variation in HDC activity in these cells is unknown, but may be attributable to differences in the stages of maturation of AB-positive cells. In fact, the HDC activity was found to be closely correlated with the percentage

of AB-positive cells in KU-812-F cell cultures (Fig. 1). The HDC activity of a crude extract of AB-positive cells is estimated to be 60 pmol/min/mg protein which is higher than that in rat stomach (10 pmol/min/mg protein), but slightly less than that in rat mast cells and fetal liver (118 and 70 pmol/min/mg protein respectively) [30, 31] under similar assay conditions.

The HDC activity of KU-812-F cells was inhibited strongly by 1.0 μM FMH, a specific inhibitor of HDC [32], but not by 1.0 μM carbidopa, a specific inhibitor of AADC (Fig. 2). Carbidopa at 10 and 100 μM inhibited HDC, but it is probably not a specific inhibitor at higher concentrations, because it has a very reactive hydrazine group and binds to the pyridoxal 5'-phosphate moiety of any pyridoxal enzyme [33]. Furthermore, when the same enzyme solution was incubated with L-DOPA, a substrate of AADC, no dopamine was formed under conditions in which an extract of rat kidney formed 7.4 nmol dopamine/min/mg protein. These results indicate that the histamine-forming activity in KU-812-F cells is due to HDC, not to AADC. This conclusion is supported by the fact that the K_m value of the enzyme in KU-812-F cells for L-histidine (0.27 mM) is similar to those of HDCs from other sources [1, 5, 31].

Maeyama *et al.* [21] reported that HDC of rat basophilic leukemia (2H3) cells could be induced by PMA, oleoyl-acetylglycerol, and cross-linked IgE. HDC induction was also observed in KU-812-F cells and took several hours to reach a maximum (Fig. 3B). Because PMA is known to activate protein kinase C [34, 35], HDC induction may be mediated by protein kinase C. This possibility is supported by the finding that staurosporine, a potent inhibitor of protein kinase C [36], blocked the increase in HDC induced by PMA (Fig. 4). Although the IC_{50} value of staurosporine seems to be somewhat higher than that reported in other systems, the intracellular concentration of staurosporine is speculated to be much lower than the extracellular one. In contrast to results in rat basophilic leukemia cells, no increase in HDC activity was observed in KU-812-F cells upon aggregation of receptors for IgE. As to the presence of surface IgE receptors on these cells, Fischkoff *et al.* [37] revealed that approximately 1×10^4 molecules of IgE bound to the cell surface with low affinity, whereas the presence of a small number of high-affinity IgE receptors could not be excluded. Furthermore, Shimizu *et al.* [38] cloned the human mast cell IgE receptor α-chain cDNA from KU-812 cells. We speculate that the failure of these cells to respond to IgE-anti-IgE reactions in histamine release and HDC induction is due to immaturity of KU-812-F cells with respect to the development of high-affinity IgE receptors and/or various intracellular enzymes that are involved in histamine release and/or HDC induction. The increase in HDC activity by PMA was due to induction of the HDC molecules, because it was blocked by cycloheximide, an inhibitor of protein synthesis (Fig. 5).

Judging from the present results, KU-812-F cells should be useful for further studies on human HDC, such as the purification of HDC, the production of anti-HDC antibody and the mechanism of HDC induction, that are under way in our laboratories.

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