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INDUCTION OF HISTIDINE DECARBOXYLASE IN RAT BASOPHILIC LEUKEMIA CELLS BY INTERFERON AND PREVENTION OF ITS EFFECT IN COINCUBATION WITH ADP-RIBOSYLTRANSFERASE INHIBITORS

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SUMMARY: Treatment of rat basophilic leukemia cell line (2H3) with interferon-alpha significantly increased intracellular histamine levels. On the other hand, the histidine content was decreased reciprocally by interferon in a dose-dependent manner. Concomitantly, the activity of histidine decarboxylase, the enzyme responsible for histamine synthesis, was augmented. The increase in histidine decarboxylase activity was partially abolished in co-incubation with inhibitors of ADP-ribosyltransferase, such as 3-aminobenzamide or nicotinamide. These results suggest the pivotal role of activation of histidine decarboxylase, presumably through ADP-ribosylation of the enzyme, in interferon-induced histamine synthesis.

Interferons (IFNs) have a wide variety of actions in addition to their antiviral or antiproliferative activities. Among them is an effect on the release and synthesis of histamine. It has been reported that IgE-mediated histamine release is enhanced when basophils are exposed to certain viruses before treatment with anti-IgE. This enhancement of histamine release was in fact attributed to IFN(s) induced by viruses, since the addition of IFN to the cultures produced similar effects (1). Moreover, we showed that

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Abbreviations: HDC, L-histidine decarboxylase; 2H3, rat basophilic leukemia (2H3) cell line; IFN, interferon; ADPRT, ADP-ribosyltransferase; 3-ABA, 3-aminobenzamide.

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recombinant IFN-alpha augmented not only histamine release by calcium ionophore A23187 but histamine synthesis itself in a rat basophilic leukemia cell line, 2H3 (2). However, the precise mechanism for this phenomenon remains to be elucidated. Exley et al. recently reported that the induction of differentiation by IFN in a B-lymphoblastoid cell line (Daudi) was impaired by inhibitors of ADP-ribosyltransferase (ADPRT) (3). This suggests the possibility that the action(s) of IFN is (are) mediated through a post-translational modification of proteins by ADP-ribosylation. Thus, in the present study, we investigated (i) the changes of histidine content and histidine decarboxylase (HDC) activity following IFN-alpha treatment and (ii) the role of ADP-ribosylation in this system by using inhibitors of ADPRT.

MATERIALS AND METHODS

Cell culture and Chemicals; 2H3 cells were maintained as described by Barsumian et al. (4). Recombinant IFN-alpha was a gift of Takeda Chemical Industries, Ltd. 3-aminobenzamide (3-ABA) was purchased from Tokyo Kasei Kogyo Co.Ltd.. Nicotinamide and other agents were obtained from Sigma.

Extraction and measurement of cellular histidine and histamine; The cells were detached by 0.25% trypsin in 0.02% EDTA phosphate-buffered saline and washed twice with ice-cold phosphate-buffered saline. The samples were extracted with 0.5N perchloric acid and immediately neutralized with 1M KOH/0.33M potassium phosphate. Histidine was determined with an automated amino acid analyzer (Waters). Histamine was assayed on high-performance liquid chromatography using postcolumn derivatization with o-phthalaldehyde (5).

Measurement of histidine decarboxylase activity; Release of $^{14}CO_2$ from L-[carboxyl-^{14}C] histidine(56mCi/mmol;Amersham Japan Corp.,Tokyo) was determined in suspensions of intact 2H3 cells(6). The final reaction mixture contained $5x10^4$ cells, 20nCi of labeled histidine (10uM), and 10uM pyridoxal phosphate in 40ul of modified Hanks' medium (Hanks' medium supplemented with 10 mM 4-(2-hydroxyethyl)-1-piperazine-ethanesulfonic acid and 0.1% bovine serum albumin) (7). Release of $^{14}CO_2$ was measured over 60 min in the presence of various concentrations of IFN.

RESULTS AND DISCUSSION

We first examined the effect of IFN on histamine synthesis in 2H3 cells. After incubation of 2H3 with various concentrations of IFN for 48 hours, intracellular histamine was measured. Histamine levels were found to increase along with the increase in IFN concentrations, which was consistent with a previous study (2).

To elucidate further the biochemical basis for this phenomenon, we evaluated the amount of intracellular histidine a precursor of histamine. Exponentially growing 2H3 cells contained 2.80±0.43 nmol histidine/10^6 cells. In the presence of IFN, the histidine content was decreased in a dose-dependent fashion, reflected by a rise in the ratio of histamine to histidine (Fig.1). IFN apparently facilitated a catalytic action from histidine to histamine, and activation of HDC was suspected.

Therefore, we examined HDC activity with intact 2H3 cells, since the activity of HDC is not detectable after

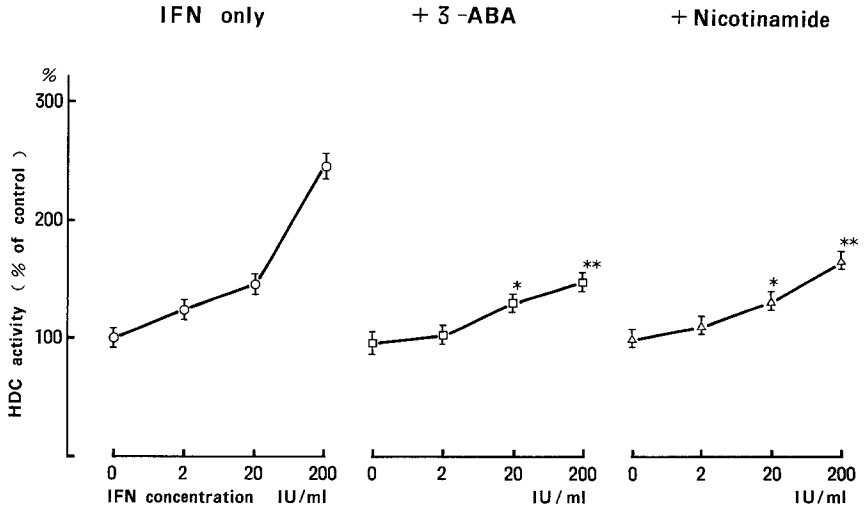

Fig.1. Dose response curve of histamine content ▨ and histidine content □ of 2H3 cells treated with IFN for 48 hours. Values are the mean±S.D. of six experiments. Histamine/histidine ratios are represented by (○).

cell destruction (8). HDC activity of control cultures was 243±26 pmol/10^6 cells/hr. After 1 hour of incubation with IFN, HDC activity was increased in accordance with the concentration of IFN (Fig.2). This effect on HDC was partially abolished by the addition of 3-ABA (5mM) or nicotinamide (5mM), inhibitors of ADPRT (9), 2 hours before IFN treatment. This result suggests the possibility that the activation of HDC by IFN is regulated partially through ADP-ribosylation of the enzyme. The above sequence of metabolic events is not specific for histamine metabolism, but is one

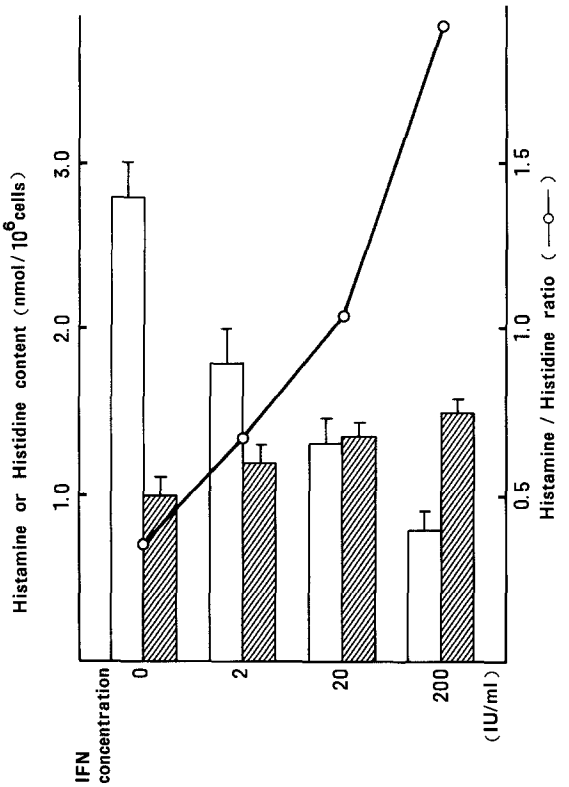

Fig.2. Changes in HDC activity caused by IFN treatment of 2H3 cells (○). 2H3 cells were treated with various concentrations of IFN for 1 hr, followed by HDC measurement as described in Materials and Methods. The average HDC activity in untreated cells was 243±26 pmol/10^6 cells/hr. Effect of inhibitors of ADPRT on IFN-induced HDC activity is shown as percentages of control activity. 5mM 3-ABA (□); 5mM nicotinamide (△). Values are the mean ± S.D. of six experiments. (*$p<0.05$, **$p<0.01$)

aspect of altered amino acid metabolism induced by IFN(s). For example, Yasui et al. noted that IFN can enhance tryptophan degradation by inducing indoleamine 2,3-dioxygenase in human lung tissues (10). In addition, the induction of ornithine decarboxylase, the rate-limiting enzyme of polyamine biosynthesis which works on ornithine as the substrate, is inhibited by IFN (11).

At any rate, our present findings shed some light on the biochemical basis for augmentation of histamine synthesis following viral infections in patients with bronchial asthma (1).

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