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SHORT COMMUNICATION

Induction by Interleukin-1 (IL-1) of the mRNA of Histidine Decarboxylase, the Histamine-Forming Enzyme, in the Lung of Mice *In Vivo* and the Effect of Actinomycin D

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ABSTRACT. It is known that the activity of histidine decarboxylase (HDC), the histamine-forming enzyme, is induced in response to various stimuli. However, it has repeatedly been reported that actinomycin D (Act D), a typical inhibitor of RNA synthesis, is either ineffective, or actually potentiates induction of this enzyme. Thus, it has been suggested that the induction of HDC may not require the formation of mRNA, i.e. that pre-formed, long-lived mRNA molecules may be responsible for the induction. In the present study, we examined the effects of interleukin-1α (IL-1α) on the amount of HDC mRNA present during the induction of HDC activity. In mice injected with IL-1α, HDC mRNA increased in the lung, spleen and stomach, but was hardly detectable in these tissues in control (saline-injected) mice. In the lung, the time course of the rise and fall in HDC mRNA was shorter than that of the rise and fall in HDC activity. In the present study, actinomycin D (Act D) did not inhibit the increase in HDC mRNA induced by IL-1α; in fact, it potentiated the elevation of both HDC mRNA and HDC activity. These results suggest that IL-1α induces HDC activity or its enzyme protein through the formation of short-lived HDC mRNA molecules. This is the first demonstration that Act D can enhance an increase in HDC mRNA: this potentiating, rather than inhibiting, effect is discussed. BIOCHEM PHARMACOL 53;9:1383–1388, 1997. © 1997 Elsevier Science Inc.

KEY WORDS. histidine decarboxylase; mRNA; histamine; interleukin-1; actinomycin D

In normal mice, the activity of histidine decarboxylase (HDC),§ the histamine-forming enzyme, is very low in tissues other than bone marrow and stomach. However, HDC has been shown to be inducible by various stimuli [1–4]. The induction of HDC occurs even in mast cell-deficient mice [5].

There have been many reports indicating that actinomycin D (Act D), a typical inhibitor of RNA synthesis, does not suppress the induction of HDC activity, although it is inhibited by inhibitors of protein synthesis [2]. On the contrary, Act D has been shown to enhance the induction of HDC activity by endotoxin or lipopolysaccharide (LPS) in various mouse tissues [6–8]. Such an inefficacy or stimulation by Act D has also been observed in studies in which an elevation of gastric HDC activity is induced in rats by gastrin, insulin, or food [9–11]. Consequently, it has been suggested that the synthesis of HDC protein may be directed by preformed, long-lived mRNA molecules [2]. However, recent studies have shown that there is an increase in HDC mRNA during the induction of HDC activity (1) in the fundus of stomach by gastrin [12], (2) in mastocytoma cells by costimulation with dexamethasone and 12-O-tetradecanoylphorbol-13-acetate [13], and (3) in bone marrow cells by interleukin-3 (IL-3) [14].

LPS is known to stimulate the production of inflammatory and hematopoietic cytokines such as interleukin-1 (IL-1), tumor necrosis factor (TNF), IL-3, granulocyte-macrophage-colony stimulating factor (GM-CSF), and granulocyte-colony stimulating factor (G-CSF), and these cytokines have been shown to induce HDC activity in the tissues of mice [15–18]. Recently, we presented a line of evidence suggesting that the major cells in which HDC activity is induced in lung and liver in response to IL-1 or TNF may be vascular endothelial cells [19]. In the present

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§ *Abbreviations:* HDC, histidine decarboxylase; IL-1, interleukin-1; Act D, actinomycin D; LPS, lipopolysaccharide; TNF, tumor necrosis factor; IL-3, interleukin-3; GM-CSF, granulocyte-macrophage-colony stimulating factor; G-CSF, granulocyte-colony stimulating factor; PCR, polymerase chain reaction.

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study, we detected HDC mRNA in the tissues of mice injected with IL-1, and examined the effect of Act D.

MATERIALS AND METHODS

Animals and Materials

Male BALB/c mice (6 weeks old) were obtained from the mouse center of our university. LPS of *Escherichia coli* O55B5, prepared by Boivin's method, was obtained from Difco Labs (Detroit, MI, USA). Recombinant human IL-1α, prepared according to the method of Furutani *et al.* [20], was provided by Dainippon Pharmaceutical (Osaka, Japan). Act D was obtained from Sigma Chemical Co. (St. Louis, MO, USA). These agents were dissolved in sterile saline and injected intraperitoneally.

Assay of HDC Activity

The mice were decapitated at the time indicated in each experiment, and the tissues were quickly removed and frozen at −80°C until use. HDC activity was assayed fluorometrically by a previously described method [21], with a slight modification [22]. HDC activity was expressed as nmol of histamine formed during a 1-hr period by the enzyme contained in 1 g of each tissue (nmol/hr/g). Values for HDC activity are given as mean ± standard deviation. Statistical significance of differences between two means were evaluated by Student's unpaired *t*-test and *P*-values less than 0.05 were considered to be significant.

Preparation of an HDC-cDNA Probe by PCR and Subcloning

Complementary DNA (cDNA) related to the liver RNA isolated from LPS-treated mice (3 hr after 0.1 mg/kg LPS) was synthesized using avian myeloblastosis (AMV) virus reverse transcriptase (Life Science Inc., St. Petersburg, FL, USA) [23]. Because sequence data for mouse HDC were not available at the beginning of this project, we designed the polymerase chain reaction (PCR) primers using the sequence of rat cDNA (1492 Nt to 2003 Nt) [24]. The oligonucleotide primers were 5′-GCTGCTAACCTT-GTCCTGAG-3′ (rat HDC-1) and 5′-CCACACT-GAGAGCTGCATTC-3′ (rat HDC-2).

The PCR was performed using 1/10 by volume of cDNA reaction mixture and 2.5 units of Taq DNA polymerase (Perkin-Elmer/Cetus, Emeryville, CA, USA) in 100 μL of reaction mixture [25]. PCR products were subcloned into the pCR1000 vector using a TA cloning kit (Invitrogen Corporation, San Diego, CA, USA). The DNA sequence was determined by the dideoxy termination method [26], using a Sequenase Version 2.0 DNA sequencing kit (United States Biochemical Corp., Cleveland, OH, USA).

Northern Blot Analysis

Tissues quickly removed from freshly killed mice and immediately frozen at −80°C were used. RNA was prepared by the guanidine thiocyanate method [27]. RNA was resolved on 1.1% formaldehyde agarose gel [28]. After electrophoresis, RNA was transferred to a nitrocellulose sheet (Schleicher and Schuell GmbH, Dassel, Germany) by a capillary method [29]. Hybridization was performed as described in our previous report [29]. The filters were washed with 5 mM Tris-HCl (pH 8.0), 0.2 mM EDTA, 0.05% sodium pyrophosphate, 0.1 × Denhardt's solution (0.002% Ficol, 0.002% polyvinylpyrolidone, 0.002% BSA), for 18 hr at 65°C, and were rehybridized with chicken β-actin [30]. The bands of HDC mRNA were analyzed quantitatively using a Fuji BAS 2000 Imaging Analyzer (Fuji Film Co., Tokyo, Japan) and the relative intensities of the bands (normalized with respect to the intensity of the corresponding β-actin) were plotted.

RESULTS

Induction of HDC mRNA by IL-1 in Various Tissues

The maximum HDC activity induced by IL-1 in lung, liver and spleen is attained 3 to 4 hr after its injection into mice [16]. In the present study, we tested for the presence of HDC mRNA 2 hr after IL-1 injection (Fig. 1). In IL-1–injected mice, HDC mRNA was detected in the lung, spleen, and stomach but was hardly detectable in the corresponding tissues of saline-injected mice. Although IL-1 can induce HDC activity in the liver, we could not detect

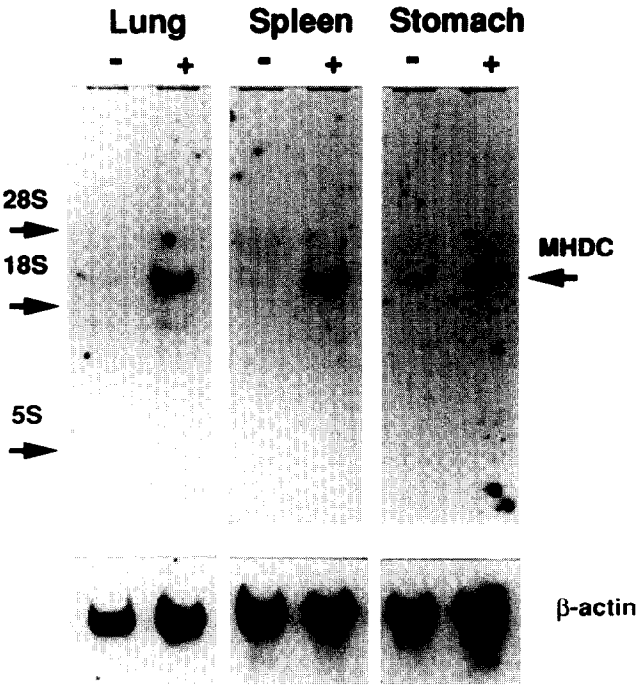

FIG. 1. Northern blot hybridization. Total RNA was isolated from the pooled tissues of four mice which were removed 2 h after injection of saline or IL-1α (10 μg/kg). Each lane contains 10 μg of total RNA. The mouse HDC probe described in the text was used in the hybridization mixture. (-), Control mice (saline-injected); (+), IL-1α–injected mice; MHDC, mouse HDC mRNA.

any increase in HDC mRNA in this tissue (data not shown), possibly because of its low content and/or degradation during the preparation. Among the tissues tested, HDC mRNA was detected most clearly in the lung. This seems likely due to the fact that the HDC activity induced by IL-1, when expressed as activity per mg protein, is higher in the lung than in any other organ [16].

Induction of HDC mRNA in Lung and Effect of Act D

Figure 2 shows the time course of the induced increases in HDC mRNA. The minor bands seen below the major bands in each lane are probably due to degradation of HDC mRNA, because there is parallelism between them. Quantitative data derived from these results are shown in Fig. 3A. After injection of IL-1 alone, HDC mRNA had increased at 1 hr, peaked at 2 hr, begun to decline at 4 hr, and had returned to a basal low level at 6 hr. Act D (1 mg/kg) did not suppress the increase in HDC mRNA induced by IL-1; on the contrary, the amount of HDC mRNA was greater than that seen in mice injected with IL-1 alone throughout the whole experimental period. Even 5 mg/kg of Act D did not suppress the increase in HDC mRNA induced by IL-1. In fact, this dose of Act D produced an even larger amount of HDC mRNA than that produced by IL-1 plus 1 mg/kg of Act D.

Induction of HDC Activity and Effect of Act D

Figure 3 shows HDC activity and the relative amounts of HDC mRNA induced in the lung by IL-1. In a manner corresponding to that of the increase in HDC mRNA, HDC activity in the lung had increased 1 hr after injection of IL-1 and had peaked by 2 to 4 hr (Fig. 3B). The HDC activity remained at a high level even at 6 hr. On the other hand, in mice injected simultaneously with IL-1 and ActD, HDC activity continued to increase for up to 6 hr and reached a markedly higher level than that induced in the mice given IL-1 alone. Such a potentiation by Act D of the effect of IL-1 on HDC activity was also seen in the liver, spleen and bone marrow (Table 1). Act D, by itself, did not enhance HDC activity.

DISCUSSION

Injection of IL-1α into mice increased HDC mRNA in the lung, spleen, and stomach. In the lung, the time course of the rise and fall in HDC mRNA was shorter than that of the rise and fall in HDC activity. Consequently, HDC mRNA had returned to a basal low level 6 hr after injection of IL-1, although a high level of HDC activity remained even at this time. It has been suggested that IL-1 is involved in many of the actions of LPS or endotoxin, because LPS is one of the most potent inducers of IL-1 and LPS and IL-1

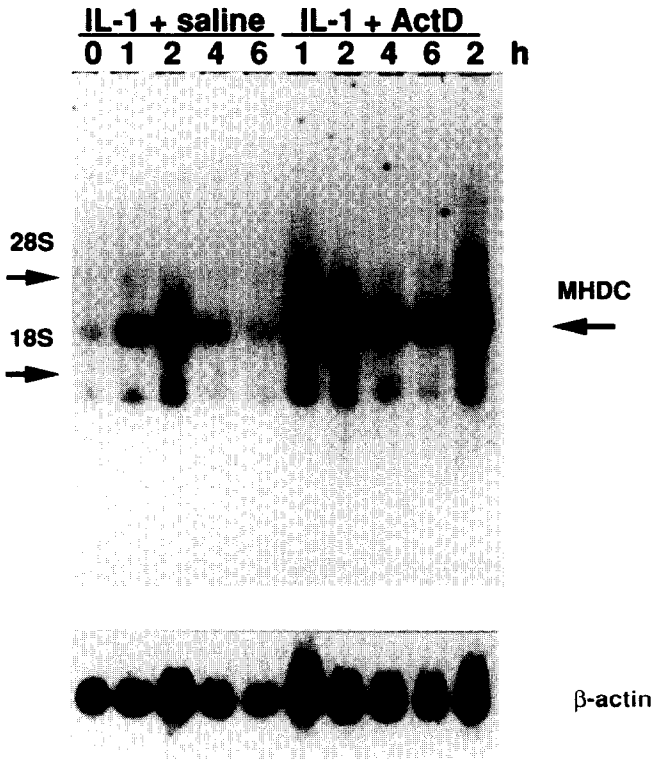

FIG. 2. Time course of the induction of mouse HDC mRNA in the lung and the effect of Act D. The number above each lane represents the time (hour) at which the lungs were removed after the simultaneous injection of IL-1α (10 μg/kg) and either saline or Act D (1 mg/kg). The lane on the extreme right shows the results when lungs were removed 2 h after injection of IL-1α with a higher dose (5 mg/kg) of Act D. Lungs from four mice were combined each time, and Northern blot hybridization was carried out as described in Fig. 1. MHDC, mouse HDC mRNA.

have most of their actions in common [31]. We confirmed that LPS (0.1 mg/kg) also increased HDC mRNA in the lung and spleen (data not shown). These results suggest that the elevation of HDC activity induced in these tissues by IL-1 or LPS is mediated through the formation of an HDC mRNA which has a short life span.

It is well known that Act D binds preferentially to DNA and inhibits RNA synthesis. As described in the introductory comments above, Act D has repeatedly been reported to be ineffective in suppressing the induction of HDC activity in various tissues. On the contrary, Act D has been shown to potentiate the induction of HDC activity in various experiments *in vivo*. We have also observed that the induction of HDC activity *in vivo* by LPS is enhanced by Act D [32].

In the present study Act D, in correspondence with its inefficacy in suppressing HDC activity, showed no suppressive effect on the increase in HDC mRNA induced by IL-1 in the lungs of mice. On the contrary, a potentiation by Act D of the increase in HDC mRNA was observed throughout the experimental period (Figs. 2 and 3). The doses of Act D administered (1 and 5 mg/kg) are larger than those capable of blocking more than 95% of RNA synthesis in the liver

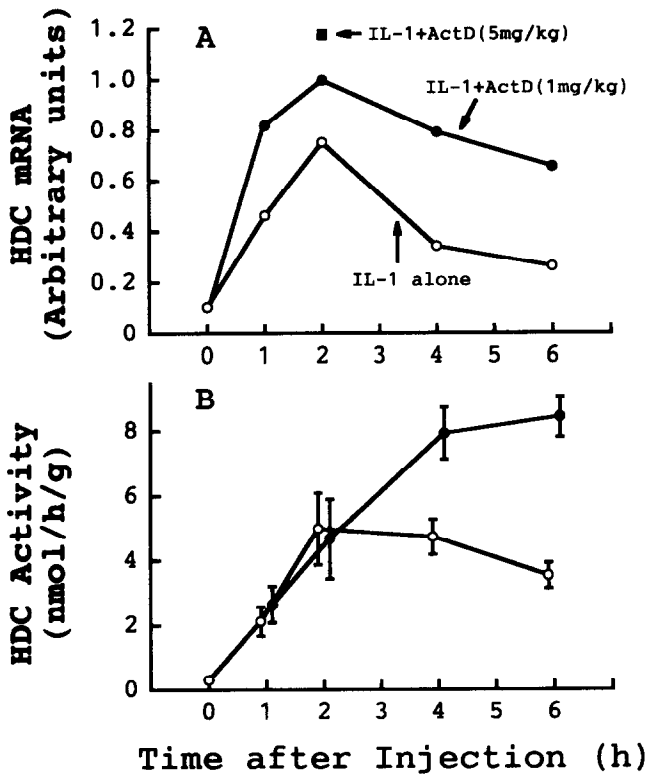

FIG. 3. Comparison of the time kinetics of the induction of HDC mRNA and HDC activity in the lung. Lungs were removed at the times indicated after injection of IL-1α (10 μg/kg) alone or simultaneous injection of IL-1α (10 μg/kg) and Act D (1 mg/kg). The relative intensities of the bands of HDC mRNA shown in Fig. 2 are plotted. Also plotted ■ is the HDC mRNA in the lungs of mice given IL-1α and 5 mg/kg Act D (see Fig. 2). The values for HDC activity are mean ± standard deviation of results from four mice.

TABLE 1. Effect of Act D on the induction of HDC activity by IL-1α

	HDC activity (nmol/hr/g)			
	Lung	Liver	Spleen	Bone Marrow
Saline	0.4 ± 0.2	0.1 ± 0.1	2.5 ± 0.3	5.4 ± 0.3
Act D alone	0.6 ± 0.2	0.4 ± 0.2	2.2 ± 0.5	6.3 ± 0.7
IL-1 alone	5.9 ± 2.2	1.6 ± 0.2	15.5 ± 3.3	17.8 ± 4.5
IL-1 + Act D	11.5 ± 1.1*	3.0 ± 0.6*	27.5 ± 2.4*	20.8 ± 4.8

Tissues were removed 4 hr after injection of saline, Act D (1 mg/kg), IL-1α (10 μg/kg) or simultaneous injection of IL-1α (10 μg/kg) and Act D (1 mg/kg). The values are mean ± standard deviation for 4 mice.

* $P < 0.05$ vs. IL-1 alone.

[33]. Indeed, 1 mg/kg of Act D is sufficient to inhibit the induction, by the oral administration of yolk, of ornithine decarboxylase (another typical inducible enzyme) in the liver of starved mice [34]. This dose of Act D can also inhibit the induction by LPS of indoleamine dioxygenase in the lungs of mice [35, 36]. In *in vitro* experiments, the induction of HDC activity in mastocytoma P-815 cells and of indoleamine dioxygenase activity in lung slices has been shown to be abolished almost completely by Act D [13, 37]. Therefore, it seemed surprising that even 5 mg/kg of Act D did not inhibit, and in fact even potentiated, the increase in HDC mRNA (Figs. 2 and 3).

We have shown that induction of HDC activity seen in the liver and lung of mice may actually occur in vascular endothelial cells [19]. On the other hand, the induction of ornithine decarboxylase in the liver by LPS may occur in hepatocytes [38], and the induction of indoleamine dioxygenase in the lung by LPS has been shown to occur in alveolar interstitial cells [39]. Therefore, a possible explanation for our present results is that Act D cannot enter vascular endothelial cells, although it can enter other cells such as hepatocytes and alveolar interstitial cells. However, this would not explain the potentiating effect of Act D. Interestingly, Leinwand and Ruddle [40] and Toku *et al.* [41] have demonstrated that Act D interacts both *in vivo* and *in vitro* with some kinds of mRNA and stimulates the activity of their template by changing its conformation. Therefore, such an action of Act D might be involved in the potentiating effect of Act D on HDC induction. It is also possible that an inhibition of the degradation of HDC mRNA might be involved. Whatever the underlying mechanisms, a solution to this problem is beyond the scope of the present study.

In conclusion, the induction by IL-1 or LPS of HDC activity or of HDC enzyme protein in some mouse tissues, at least in the lung, is mediated by newly formed, short-lived HDC mRNA, not by preformed, long-lived HDC mRNA. The explanation for the potentiation by Act D of the increase in HDC mRNA remains unclear.

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