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Effects of macrophage depletion on the induction of histidine decarboxylase by lipopolysaccharide, interleukin 1 and tumour necrosis factor

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1 Our previous work has shown that injection into mice of lipopolysaccharide (LPS) and the cytokines interleukin 1 (IL-1) and tumour necrosis factor (TNF) induces histidine decarboxylase (HDC), the enzyme forming histamine, in various tissues such as liver, lung, spleen and bone marrow, but not in the blood. The induction of HDC also occurs in nude mice and mast cell-deficient mice. On the other hand, haematopoietic cytokines such as IL-3, granulocyte colony-stimulating factor (G-CSF) and granulocyte–macrophage CSF (GM-CSF) only induce HDC in the haematopoietic organs, i.e. bone marrow and spleen. In the present study, the effect of macrophage depletion on the induction of HDC was examined.

2 On day 1 after a single intravenous injection of a macrophage depletor (liposomes encapsulating dichloromethylene diphosphonate, which is toxic when ingested into macrophages), macrophages were almost completely depleted in the liver and reduced by about 50% in the spleen and bone marrow, but not significantly affected in the lung. On day 3, the degrees of the depletion were similar to those of day 1. In the spleen, macrophages were depleted in the red pulp, and there was a structural destruction.

3 In macrophage-depleted mice, the induction of HDC by LPS, IL-1α or TNF-α was not impaired in the liver, and was potentiated in the lung and bone marrow. The induction of HDC was decreased only in the spleen at day 3.

4 HDC was not induced by LPS in the spleen of the adult rat, which is correspondingly inactive in haematopoiesis.

5 These results indicate that the major cells in which HDC activity is induced in response to LPS, IL-1 and TNF are not circulating granulocytes, circulating monocytes, T cells derived from thymus, mast cells or phagocytic macrophages. Based on these results, we discuss the possibility that the major cells in which HDC was induced in non-haematopoietic and haematopoietic organs were endothelial cells and haematopoietic precursor cells respectively.

Keywords: Histidine decarboxylase; interleukin 1; cytokines; lipopolysaccharide; macrophages

Introduction

Histamine affects the microcirculation by stimulating endothelial cells to increase capillary permeability and by stimulating microvascular smooth muscles to dilate them. The inflammatory response reflects these changes and is characterized by an increased capillary permeability and an increased blood flow in fine blood vessels caused by a capillary dilatation. We have shown that the activity of histidine decarboxylase (HDC), the enzyme forming histamine, is increased in the liver, lung, bone marrow and spleen in response to lipopolysaccharide (LPS), inflammatory mitogenic agents (Endo, 1982; 1983a) and cytokines such as IL-1 and TNF (Endo, 1989; Endo *et al.*, 1986; 1992a). As these tissues have a well-developed microcirculation, it is expected that, in addition to the release of histamine from mast cells or basophils, the newly formed histamine produced by the increased HDC activity may be involved in the activation of the microcirculation. Because the increase in HDC activity is accompanied by a rapid increase in mRNA for HDC (unpublished data), this increase is due to the induction of the HDC enzyme itself.

Histamine has also been shown to stimulate *in vitro* haematopoietic precursor cells such as granulocytic precursor cells or IL-3-responder cells (Byron, 1977; Nakaya & Tasaka, 1988; Shounan & You-Heng, 1988; Schneider *et al.*, 1990). In contrast to the induction of HDC in various tissues by LPS, IL-1 and TNF as described above, the haematopoietic cytokines IL-3, GM-CSF and G-CSF induce HDC preferentially in the haematopoietic organs, i.e. bone marrow and spleen (Lebel *et al.*, 1990; Endo *et al.*, 1992a). These results suggest that histamine is involved in the proliferation or differentiation of some haematopoietic precursor cells.

Apart from IL-3, other cytokines capable of inducing HDC (i.e. IL-1, TNF, GM-CSF and G-CSF) are known to be produced mainly by macrophages and endothelial cells (Oppenheim *et al.*, 1986; Beutler & Cerami, 1987; Dinarello, 1991). Correspondingly, the organs in which HDC is induced are the tissues rich in these cells, and LPS is known to be a potent stimulator of these cells to produce the cytokines described above. Therefore, macrophages or endothelial cells may be important in the induction of HDC.

Van Rooijen *et al.* (1989, 1990) have reported that intravenous injection of dichloromethylene diphosphonate, which was encapsulated in liposomes, can deplete macrophages from the liver and spleen. In the present study, therefore, the effect of the macrophage depletor on the induction of HDC by LPS, IL-1 and TNF was examined.

Materials and methods

Animals and materials

Male BALB/c mice (6 weeks old) were obtained from the mouse centre of our university. Wistar rats (7 weeks old)

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were obtained from Japan SLC (Shizuoka, Japan). LPS of *Escherichia coli* 055B5, prepared by Boivin's method, was obtained from Difco Labs (Detroit, MI, U.S.A.). Recombinant human IL-1α and recombinant human TNF-α, which were prepared according to Furutani *et al.* (1985) and Yamada *et al.* (1985), were provided by Dainippon Pharmaceutical (Osaka, Japan). Dichloromethylene diphosphonate was provided by Kissei Pharmaceutical (Matsumoto, Japan). Reagents and cytokines were dissolved in sterilized saline and injected intravenously (i.v.) or intraperitoneally (i.p.) (0.1 ml per 10 g body weight).

Depletion of macrophages from the liver

Suspensions of liposomes encapsulating dichloromethylene diphosphonate (Cl_2MDP-liposomes) were prepared according to Van Rooijen *et al.* (1989, 1990). Briefly, 75 mg of phosphatidylcholine and 11 mg of cholesterol were dissolved in chloroform in a round-bottom flask. The thin film that formed on the walls of the flask after rotary evaporation at 37°C was dispersed by gentle shaking for 10 min in 10 ml of Cl_2MDP solution (200 mg ml^{-1}) in 10 mM sodium phosphate buffer (PBS, pH 7.4). This suspension was kept for 2 h at room temperature and sonicated for 3 min (50 Hz) and kept for another 2 h. The resulting liposomes were centrifuged at 100,000 *g* for 30 min. The volume of precipitated liposomes was about 0.5 ml, which contained a maximum of 100 mg of Cl_2MDP. The liposomes were finally suspended in 4 ml of PBS, and this preparation was injected intravenously into the tail vein (0.2 ml per mouse) within 3 days.

Detection of macrophages

Macrophages were detected by immunohistochemical staining of F4/80 antigen which is expressed specifically on the surface of these cells (Austyn & Gordon, 1981; Hirsch *et al.*, 1981). Monoclonal antibody to F4/80 antigen was purchased from SEROTEK (Kindlington, U.K.).

Tissues were fixed with 4% paraformaldehyde in PBS. After washing with PBS, specimens were immersed in 20% sucrose in PBS, embedded in Cryoform (International Equipment, Needham, MA, U.S.A.) and quickly frozen in an acetone–dry ice mixture. After the fixation, tibias were decalcified in 15% EDTA in PBS, washed with 20% sucrose in PBS, embedded in Cryoform and quickly frozen in an acetone–dry ice mixture. Frozen sections (8 μm thick) were cut, placed on poly-L-lysine-coated glass slides and air dried. After incubation in 0.3% H_2O_2-methanol for 30 min, sections were incubated in 5% normal goat serum in PBS containing 5% bovine serum albumin and 0.025% Triton X-100, then incubated with an F4/80 monoclonal antibody. After several rinses, sections were incubated with a biotinylated goat anti-rat IgG antibody (Cappel, West Chester, PA, U.S.A.), followed by incubation with ABC (avidin–biotin complex) reagent (Vector Lab., Burlingame, CA, U.S.A.). After washing, sections were treated with a mixture of 0.05% 3,3-diaminobenzidine and 0.005% H_2O_2 in Tris–HCl buffer (0.05 M, pH 7.6). Counter-staining was produced with methyl green. As controls, sections were incubated with either normal rat serum or PBS instead of the primary antibody.

Electron microscopy

The livers were removed rapidly from decapitated mice and electron microscopic analysis was carried out as described previously (Endo & Nakamura, 1992).

Assay of HDC activity

HDC activity was assayed by a previously described method (Endo, 1983b) with a slight modification (Endo *et al.*, 1992b). HDC activity in the liver, lung and spleen was expressed as nmol of histamine formed during 1 h by the enzyme contained in 1 g of each tissue (nmol h^{-1} g^{-1}). HDC activity in the bone marrow was expressed as the activity of 1 g of the tibia plus femur, because these bone tissues themselves were subjected to the assay of HDC activity (Endo *et al.*, 1992b).

Data analysis

Experimental values are given as mean ± standard deviation. Statistical significance of differences between two means of data were evaluated by Student's unpaired *t*-test, and *P*-values less than 0.05 were considered to be significant.

Results

Depletion of macrophages

On day 1 after a single intravenous injection of Cl_2MDP-liposomes, F4/80-positive macrophages were almost completely depleted in the liver (Figure 1a and b). In the spleen and bone marrow, depletion of the macrophages was about 50% (Figure 1c–f). In the spleen, macrophages were depleted in the region of the red pulp. On day 3, the degrees of the depletion in the liver, spleen and bone marrow were similar to those observed on day 1. These results are essentially the same as those observed by Van Rooijen *et al.* (1989, 1990). There was no apparent depletion of macrophages in the lung on either day 1 or day 3.

In spite of the drastic depletion of macrophages in the liver, no other histochemical changes were observed in this organ. Electron microscopic analysis indicated that endothelial cells were not decreased in the liver of mice treated with the liposome (Figure 2). In addition, there was no loss of body weight and no apparent sign of illness or weakness in the mice. There was a structural destruction only in the red pulp in the spleen (Figure 3) and a slight decrease in its weight on day 3 (about 20%).

Effect of macrophage depletion on the induction of histidine decarboxylase

Injection of LPS into mice induced a marked increase in HDC activity in the liver, lung, spleen and bone marrow of control mice treated with saline. On day 1 after injection of the liposomes, the induction of HDC by LPS was not decreased and was, in fact, enhanced in the lung and bone marrow (Figure 4).

Both IL-1 and TNF can also induce HDC, and this induction is potentiated by their combination (Endo, 1989). As shown in Figure 5, a combination of 10 μg kg^{-1} of each of IL-1 and TNF induced HDC activities similar to those evoked by 0.1 mg kg^{-1} LPS. On day 3 after injection of the liposomes, the induction of HDC by LPS or by the cytokines was not decreased in the liver, lung and bone marrow, and was again enhanced in the lung and bone marrow as observed on day 1. A significant decrease in the induction of HDC by LPS or by the cytokines was observed only in the spleen.

Comparison of the induction of histidine decarboxylase activity by lipopolysaccharide in mice and rats

Compared with the experiments described above, a large dose of LPS (1 mg kg^{-1}) was injected into rats and mice. As shown in Figure 6, LPS induced HDC in a number of tissues of these animals. However, while there was a large increase in the level of the enzyme in the spleen of mice, there was no increase in HDC activity in the spleen of rats, even by the large dose of LPS used in this experiment.

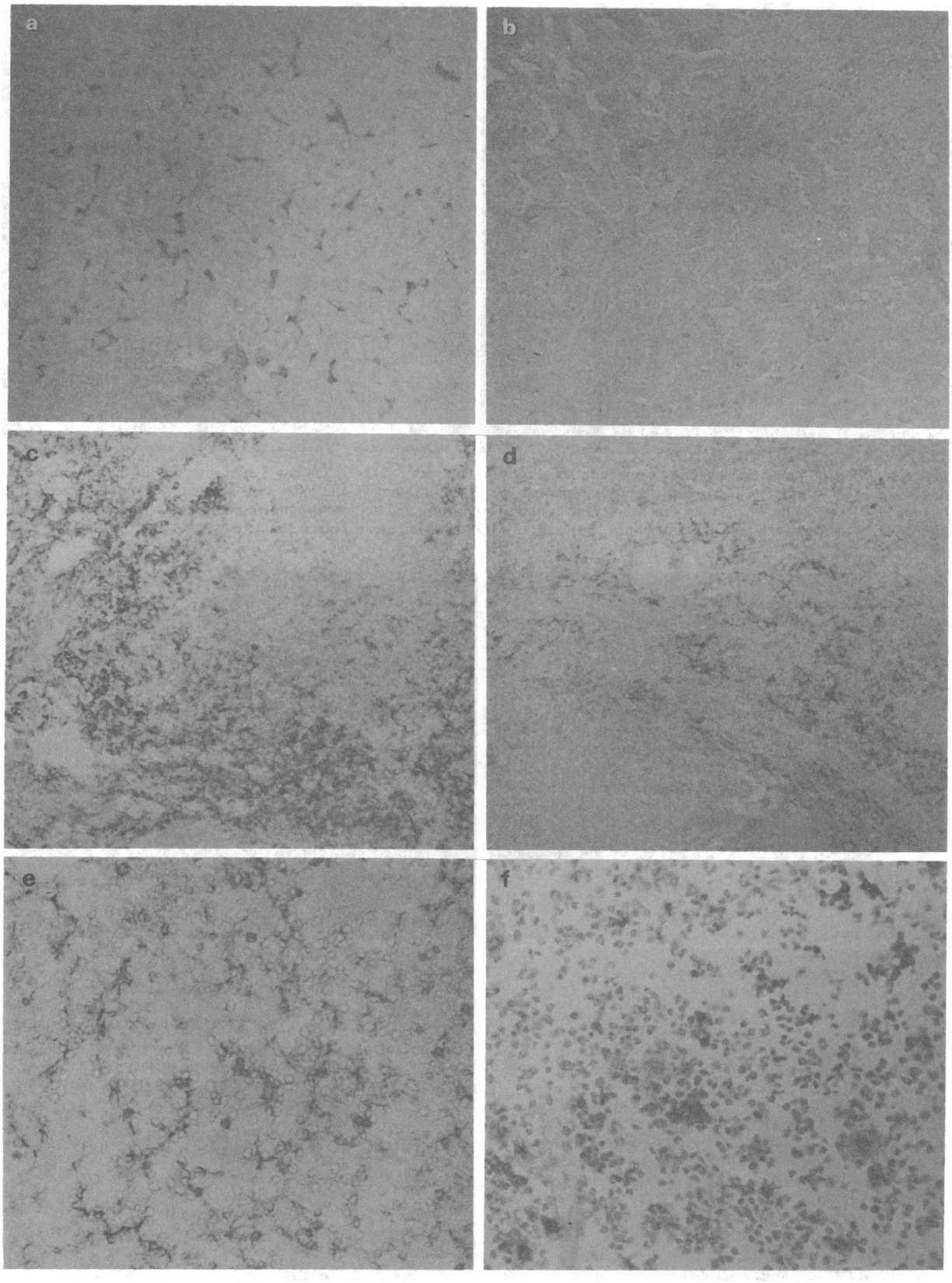

Figure 1 Effect of a macrophage depletor on mouse tissues on day 1 after its injection (× 180). On day 1 after intravenous injection of saline or liposomes encapsulating dichloroethylene diphosphonate (Cl_2MDP-liposomes), the liver, spleen and tibia were subjected to immunohistochemical staining for F4/80 antibody. There are many F4/80-positive cells in the normal liver (a), spleen (c) and bone marrow of tibia (e). In the mice treated with Cl_2MDP-liposomes, these cells are almost completely depleted in the liver (b) and reduced by about 50% in the spleen (d) and bone marrow of tibia (f).

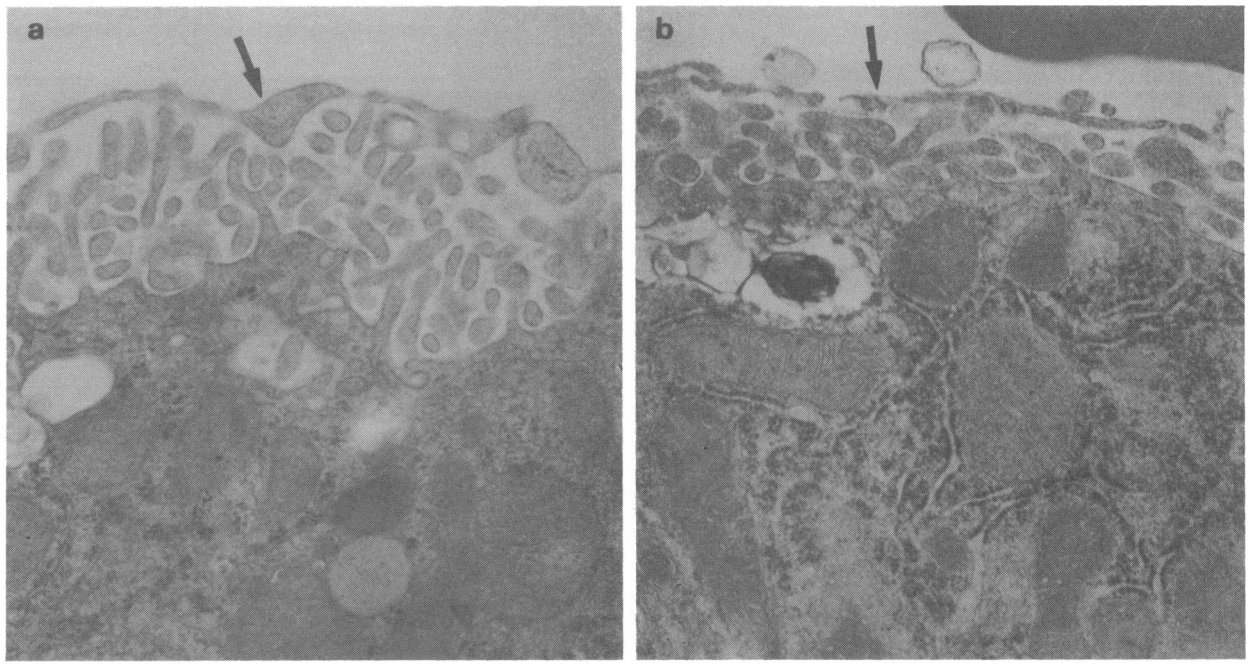

Figure 2 Effect of a macrophage depletor on endothelial cells in the liver (× 21,000). On day 3 after intravenous injection of saline or liposomes encapsulating dichloroethylene diphosphonate (Cl_2MDP-liposomes), the mice were injected with lipopolysaccharide (0.1 mg kg^{-1}, i.p.) and, 4.5 h later, the livers were removed and subjected to electron microscopic analysis. Endothelial cells (indicated by arrows) are seen in both control (a) and Cl_2MDP-liposome-treated mice (b).

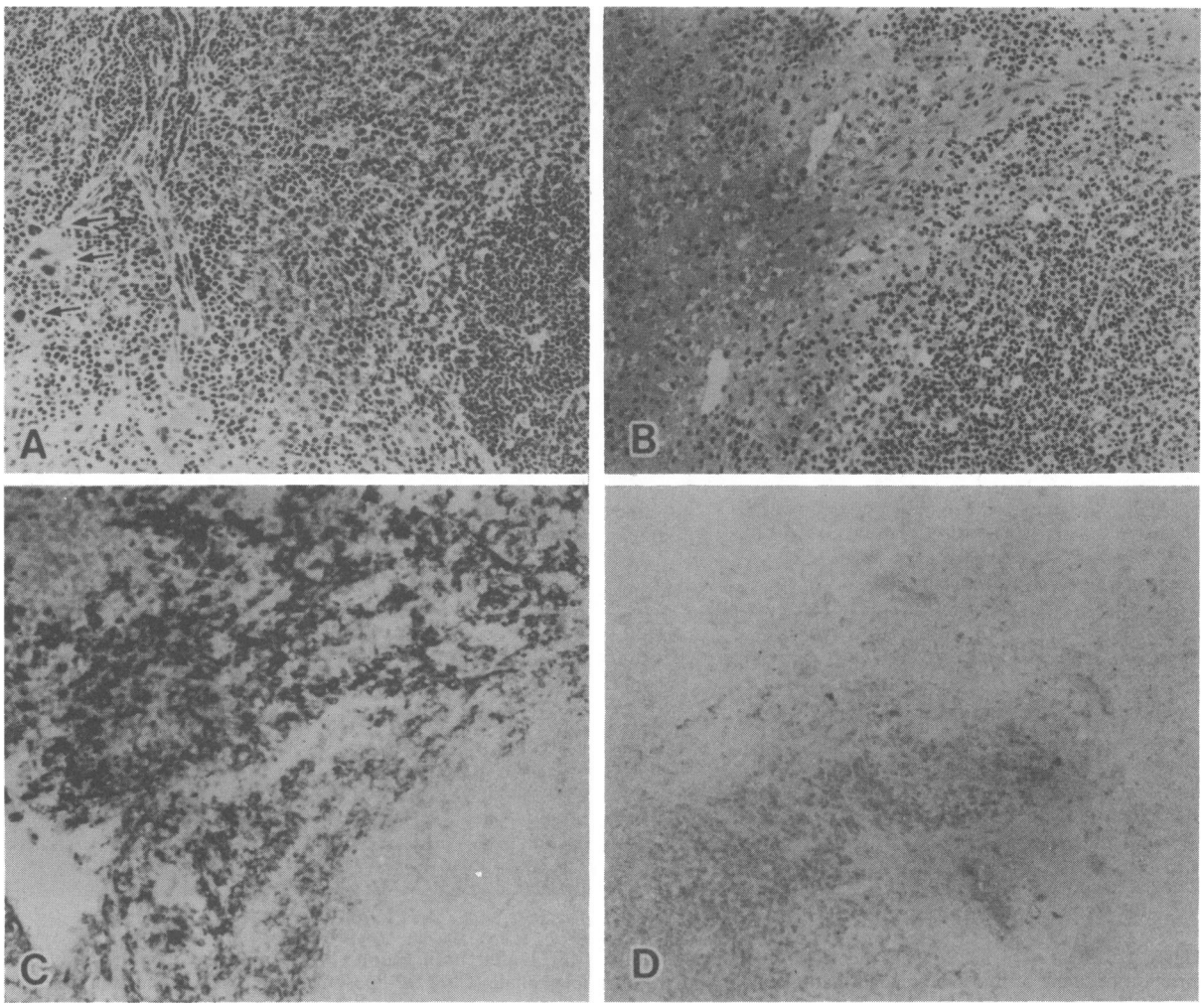

Figure 3 Effect of a macrophage depletor on the structure of the red pulp in the spleen of mice (× 180). On day 3 after intravenous injection of saline or liposomes encapsulating dichloroethylene diphosphonate (Cl_2MDP-liposomes), the spleens were subjected to haematoxylin–eosin staining (A and B) and immunohistochemical staining for F4/80 (C and D). (A) There are many cells including megakaryocytes (arrows) in the red pulp of the control mice. (B) Cells are distributed sparsely in the red pulp of the mice treated with Cl_2MDP-liposomes, and there are no megakaryocytes. (C) There are many F4/80-positive cells in the red pulp of the control mice. (D) There are no F4/80-positive cells in the red pulp of the mice treated with Cl_2MDP-liposomes.

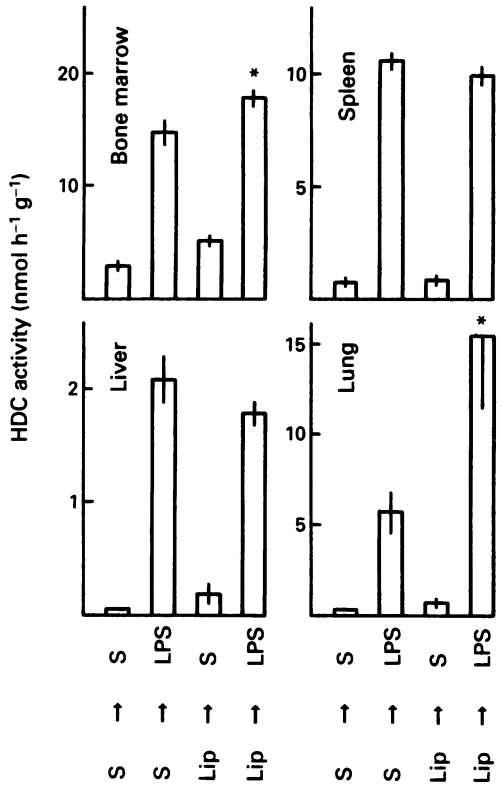

Figure 4 Induction of histidine decarboxylase (HDC) on day 1 after injection of a macrophage depletor. On day 1 after intravenous injection of saline (S) or liposomes encapsulating dichloroethylene diphosphonate (Lip), the mice were injected with lipopolysaccharide (LPS, 0.1 mg kg^{-1}, i.p.) and, 4.5 h later, tissues were removed and HDC activities were measured. Each value is the mean ± s.d. of four mice. *$P<0.05$ vs saline LPS.

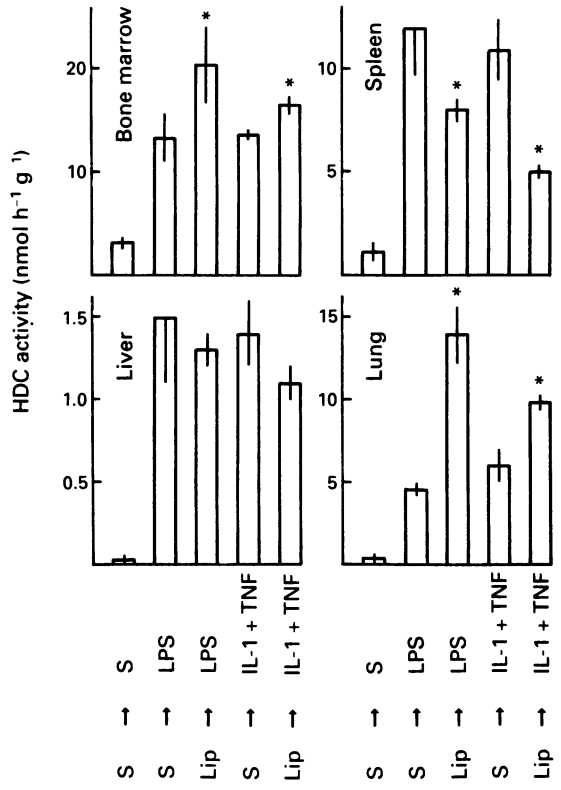

Figure 5 Induction of histidine decarboxylase (HDC) on day 3 after injection of a macrophage depletor. On day 3 after intravenous injection of saline (S) or liposomes encapsulating dichloroethylene diphosphonate (Lip), the mice were injected with lipopolysaccharide (LPS, 0.1 mg kg^{-1}, i.p.) or IL-1α plus TNF-α (10 μg kg^{-1} each, i.p.) and, 4 h later, tissues were removed and HDC activities were measured. Each value is the mean ± s.d. of four mice. *$P<0.05$ vs saline LPS or saline IL-1 + TNF.

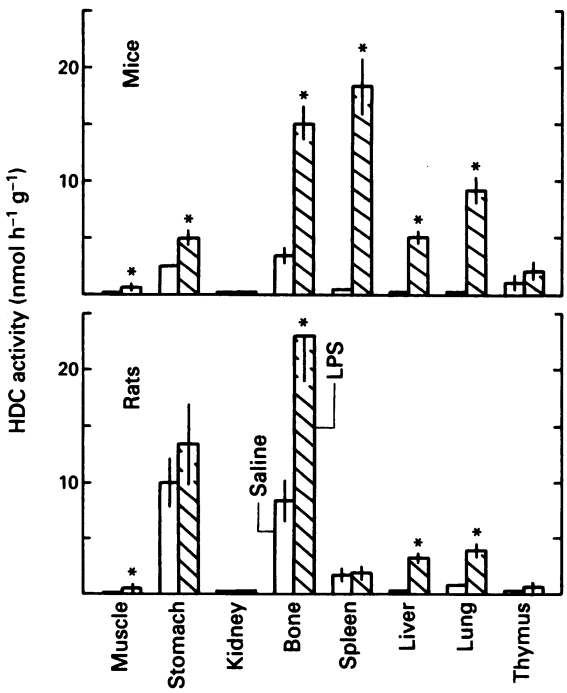

Figure 6 Comparison of the induction of histidine decarboxylase (HDC) between mice and rats. Mice (6 weeks old) and rats (7 weeks old) were injected with saline (open columns) or lipopolysaccharide (hatched columns, 1 mg kg^{-1}, i.p.) and, 4.5 h later, their tissues were removed and HDC activities were measured. Each value is the mean ± s.d. of four mice. *$P<0.05$ vs control (saline injected).

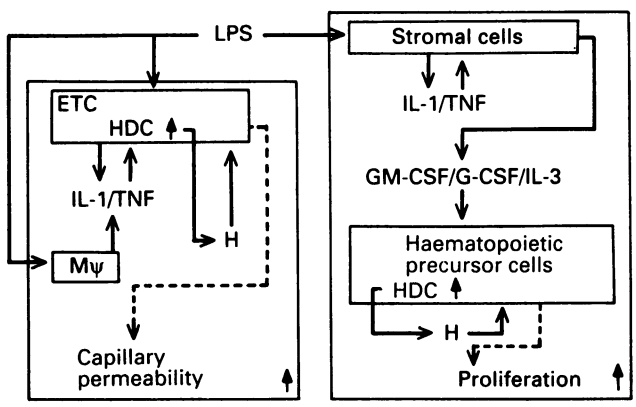

Figure 7 Hypothetical schema of the induction of histidine decarboxylase (HDC) in response to lipopolysaccharide (LPS). In non-haematopoietic organs such as the liver, lung and skeletal muscle (left), LPS stimulates endothelial cells (ETC) and/or macrophages (Mψ), resulting in a production of IL-1 and/or TNF. These cytokines stimulate the ETC and induce HDC within them. The newly formed histamine also stimulates the ETC, resulting in an enhanced capillary permeability. In haematopoietic organs (right), LPS stimulates stromal cells to produce IL-1 and/or TNF. These cytokines stimulate the stromal cells and result in production of GM-CSF, G-CSF and IL-3. These cytokines stimulate haematopoietic precursor cells and induce HDC in these cells. The newly formed histamine stimulates the haematopoietic precursor cells themselves to stimulate their proliferation.

Discussion

We have shown that injection into mice of various inflammatory mitogenic substances such as LPS and concanavalin A (Endo, 1983a) or cytokines such as IL-1, TNF, G-CSF and GM-CSF (Endo, 1989; Endo *et al.*, 1986, 1992a) induces HDC in various tissues. HDC activities are also increased by LPS in nude mice to similar extents as in normal controls (Endo, 1983a). W/W^V mice are known to be deficient in mast cells, but LPS also induces HDC activity in these animals to a rather greater extent than in controls (Endo & Nakamura, 1993). These results indicate that neither lymphocytes derived from the thymus (i.e. T-cells) nor mast cells are the major cells involved in the induction of HDC. Hepatocytes are similarly not the major cells involved in the induction of HDC in the liver, because inhibition of RNA synthesis in these cells does not decrease the induction of HDC in this organ, although the induction of ornithine decarboxylase is strongly inhibited (Endo *et al.*, 1992c). In addition, the experiment on the isolation of liver cells indicated that the increase in histamine after injection of LPS occurred largely in cells other than hepatocytes (Endo & Nakumura, 1993).

The increase in HDC activity is most marked in the tissues rich in macrophages and endothelial cells, such as liver, lung, spleen and bone marrow. Macrophages and endothelial cells are known to be the major cells which produce the cytokines capable of inducing HDC, i.e. IL-1, TNF, G-CSF and GM-CSF. It is also possible that HDC is induced within these cells.

F4/80 antigen has been shown to be present specifically on the surface of macrophages, but not on neutrophils, mast cells, eosinophils, lymphocytes, dendritic cells, fibroblasts, erythrocytes, platelets and immature precursor cells of macrophages and neutrophils (Austyn & Gordon, 1981; Hirsch *et al.*, 1981). Within 24 h of a single intravenous injection of Cl_2MDP-liposomes, F4/80-positive macrophages were almost completely depleted in the liver, reduced by about 50% in the spleen and bone marrow, but not affected in the lung. When Cl_2MDP-liposomes are administered intratracheally, alveolar macrophages have been shown to be eliminated (Thepen *et al.*, 1989). On day 3, the degrees of the depletion in these tissues were similar to those observed on day 1. There were no other noticeable changes in these tissues of the mice given Cl_2MDP-liposomes except for the spleen. In the spleen on day 3, there was a slight decrease in its weight. Macrophages in the spleen decreased in the red pulp as observed by Van Rooijen *et al.* (1989). Histochemical staining of the spleen indicated a structural destruction of the red pulp. An electron microscopical examination indicated that endothelial cells in the liver are normal after injection of Cl_2MDP-liposomes.

In spite of complete depletion of macrophages or Kupffer's cells in the liver, the induction of HDC by LPS or IL-1 plus TNF was not impaired on either day 1 or day 3. In the lung and bone marrow, the HDC induction by LPS or IL-1 plus TNF was actually enhanced in the mice treated with Cl_2MDP-liposomes on both day 1 and day 3. There was a decrease in the induction of HDC only in the spleen on day 3. However, there was no reduction of HDC induction in the spleen on day 1 when about 50% of its macrophages had been depleted. These results suggest that the reduction of HDC induction in the spleen on day 3 is not due to the decrease in macrophages. Therefore, phagocytic macrophages located at the sites where they are exposed to Cl_2MDP-liposomes and eliminated from tissues are not the major cells in which HDC is induced. In addition, these results also indicate that the phagocytic macrophages are not the major cells which produce the cytokines capable of inducing HDC in response to LPS.

As HDC activity is not detected in the blood even after injection of LPS (Endo, 1982), circulating or mature granulocytes and circulating macrophages (i.e. monocytes) are not the cells in which HDC is induced. The present results, however, do not rule out a possible involvement of non-phagocytic or F4/80-negative macrophages.

The tissues in which HDC is induced have well-developed microvascular systems. Histamine activates endothelial cells to enhance capillary permeability and induces capillary dilatation to increase blood flow. These are essential mechanisms in inflammation for supplying or exchanging various substances and enabling immune cells to move outside the blood vessels. We have observed that forced walking for long hours or *in situ* electric stimulation of skeletal muscles of mice induces a marked HDC activity in the skeletal muscles (unpublished data). In order to keep the mobility of the skeletal muscles or to recover from fatigue, enhanced microcirculation may be required in the skeletal muscles. Schayer (1962), who found that HDC was an inducible or adaptive enzyme, has suggested that the induced histamine that is produced by the induction of HDC is an intrinsic regulator of the microcirculatory system. Although it is speculative at present, our results suggest that endothelial cells may be the major cells involved in the induction of HDC in tissues such as the liver, lung and skeletal muscles. IL-1 and/or TNF derived from endothelial cells (or non-phagocytic macrophages) may induce HDC in the endothelial cells. In addition, endothelial cells may stimulate themselves by producing histamine through the induction of HDC, implying an autocrine or paracrine mechanism.

It is also possible that the newly formed histamine may be utilized in the regulation of various immune responses (Beer *et al.*, 1984), including haematopoiesis. It is known that haematopoiesis in the spleen is inactive in adult rats. In correspondence with this, HDC induction by LPS did not occur in the spleen of adult rats. The red pulp in the spleen of mice is the site of haematopoiesis. The reduction in HDC induction observed in the spleen on day 3 after injection of Cl_2MDP-liposomes may be due to a structural destruction of the red pulp, i.e. an impaired haematopoiesis. In addition, haematopoietic cytokines, IL-3, G-CSF and GM-CSF, induce HDC only in the haematopoietic organs of mice (Lebel *et al.*, 1990; Endo *et al.*, 1992a). Therefore, these results suggest that haematopoietic cells or stromal cells are involved in the induction of HDC in haematopoietic organs. The term 'stromal cells' is the generic name for various cells which support haematopoiesis and includes endothelial cells, macrophages and fibroblasts. Stromal cells are known to produce IL-3, G-CSF and GM-CSF in response to LPS, IL-1 and TNF (Dorshkind, 1990). Because spleens of adult rats contain endothelial cells, macrophages and fibroblasts, it seems unlikely that stromal cells are the cells in which HDC is induced. Therefore, the most likely cells in which HDC is induced in the spleen and bone marrow seem to be haematopoietic precursor cells.

Histamine stimulates proliferation of haematopoietic precursor cells, such as granulocytic precursor cells or IL-3 responder cells (Byron, 1977; Shounan & You-Heng, 1988; Nakaya & Tasaka, 1988; Schneider *et al.*, 1990). In addition, we have shown that a prolonged enhancement of HDC activity accompanies an increase in granulocytes, macrophages and osteoclasts (Endo *et al.*, 1993), whose precursor cells are known to be identical. Therefore, we expect that HDC is induced in these haematopoietic precursor cells and that newly formed histamine may stimulate the cells themselves, again implying an autocrine or paracrine mechanism.

In conclusion, the major cells in which HDC is induced in response to LPS, IL-1 and TNF are cells other than T-cells, mast cells, phagocytic macrophages, mature granulocytes, circulating monocytes and hepatocytes. The most likely candidate in the liver, lung and skeletal muscles appears to be endothelial cells. On the other hand, in the haematopoietic organs, the candidate seems to be haematopoietic precursor cells. These hypotheses are summarized in Figure 7. We are currently attempting to visualize the cellular distribution of

HDC mRNA by *in situ* hybridization techniques but have encountered difficulties owing to the low content of the RNA.

Finally, it is necessary to consider the significance of the induction of HDC. As pharmacological administration of histamine produces shock, histamine has been believed to be an important mediator of shock syndromes. Therefore, the induction of HDC appears to contribute in the development of endotoxin shock or septic shock, because LPS is a potent inducer of HDC. Galactosamine is known to sensitize experimental animals to the lethal effect of LPS, and their combined administration produces severe congestion in the liver, resulting in a rapid death. We have shown that galactosamine enhances the LPS-induced elevation of hepatic HDC activity in mice (Endo *et al.*, 1992c). However, even a complete inhibition of the HDC activity by an irreversible inhibitor of the enzyme prevented neither the hepatic congestion nor the death, indicating that the induction of HDC is not involved in the hepatic congestion. Neugebauer *et al.* (1987) have also shown that histamine is not a predominant factor in the lethal outcome of endotoxin shock in rats induced by a large amount of LPS alone.

Major actions of histamine, such as dilatation and increased permeability of capillary vessels, stimulation of sensory nerve endings producing itch and pain and stimulation of gastric acid secretion, are responses to exogenous stimuli or materials. IL-1, IL-3, GM-CSF and G-CSF, i.e. HDC-inducing cytokines, are important factors triggering non-specific immune responses and stimulating proliferation of various immune cells. Therefore, it seems likely that the induction of HDC is an event in self-defence mechanisms.

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