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Granulocyte-macrophage colony-stimulating factor enhances interleukin-1β stimulated histamine release in the preovulatory rat ovary

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Abstract

The existence of immune cells including macrophages and mast cells in rat ovary implies that various cytokines from these cells may play a role in ovarian functions. The aim of the present study was to investigate whether granulocyte-macrophage colony stimulating factor (GM-CSF) and interleukin-1β are capable of stimulating histamine release and steroidogenesis in rat ovary, and to determine the sites of histamine production in the ovary. Histamine release from preovulatory ovarian tissues was stimulated in a dose-dependent manner at 3–30 ng/ml of GM-CSF in the presence of interleukin-1β (10 ng/ml). However, treatment with GM-CSF and interleukin-1β did not cause any significant change in the levels of ovarian steroids. Intense staining of histidine decarboxylase in the ovary was immunohistochemically detected in large granular cells on the morning of the pro-oestrus day. These results indicate that GM-CSF may be involved in the regulation of ovarian histamine secretion in mast cells partially by enhancing interleukin-1β-induced histamine release in the process of ovulation.

Keywords: GM-CSF (granulocyte-macrophage colony stimulating factor); Ovary; Histamine; Histidine decarboxylase

1. Introduction

Rodent ovary produces various cytokines which may be involved in the regulation of ovarian functions during the oestrous cycle and pregnancy. We have recently shown that granulocyte-macrophage colony-stimulating factor (GM-CSF), which is one of the important regulators for hematopoiesis and the immune system (Gasson, 1991), is expressed by ovarian theca-interstitial tissues, macrophages and mast cells in rodent ovary and the expression of mRNA for the GM-CSF receptor was found in toluidine blue-positive cells (probably mast cells) and luteal tissues in the ovary (Tamura et al., 1998). It is known that GM-CSF is synthesized in mature hematopoietic and immune cells, including mast cells (Wodnar-Filipowicz et al., 1989; Okayama et al., 1995) as well as in hemopoietic progenitor cells, and that uterine GM-CSF is closely associated with the successful establishment of pregnancy (Wegmann et al., 1989; Robertson et al., 1999). However, the physiological significance of GM-CSF production in the ovary has not been investigated.

Mast cells may release histamine on the pro-oestrus day (Krishna and Terranova, 1985). Ovarian hyperemia at the time of ovulation is an indicator of luteinizing hormone (LH) surge and the relationship between the induction of ovarian edema and histamine production has been reviewed (Krishna et al., 1989). The effects of LH, histamine and antagonists for histamine on the occurrence of ovulation have been investigated using in vitro perfused ovary (Schmidt et al., 1986, 1988). LH and histamine induced approximately 7 and 2.3 oocytes per ovary, respectively, whereas simultaneous treatment with pyrilamine and cimetidine completely inhibited the compound 48/80-induced ovulation.

Human interleukin-1β potentiates histamine release from basophils and mast cells (Subramanian and Bray, 1987; Massey et al., 1989) and induces histidine decarboxylase activity in some mouse tissues (Endo, 1989). Further, interleukin-1β has been shown to be synthesized in ovarian theca-interstitial and luteal tissues and ovarian macrophages (Simon et al., 1994). The preovulatory LH

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surge induces mRNA for ovarian interleukin-1β (Hurwitz et al., 1992). In ovarian granulosa cells, induction of LH receptor was markedly suppressed by treatment with interleukin-1β (Gottschall et al., 1987). This cytokine may modulate cyclic changes in ovarian functions, such as ovulation and luteinization, by affecting the growth and differentiation of ovarian cells (Adashi, 1990). These observations suggest possible roles for interleukin-1β as an intraovarian regulator of ovarian functions.

In the present study, therefore, we examined the effects of GM-CSF and/or interleukin-1β on ovarian histamine secretion and on steroidogenesis in ovarian cells in vitro, and studied the localization of histidine decarboxylase in the ovary, to determine the involvement of GM-CSF in the secretion of ovarian hormones.

2. Materials and methods

2.1. Animals and preparation of ovarian tissues and cells

Twenty-one-day-old immature female rats of the Wistar–Imamichi strain (Imamichi Institute for Animal Reproduction, Ibaraki-ken, Japan) were maintained under controlled temperature (23 ± 1°C), humidity (55 ± 5°C), and a 12:12-h light–dark lighting schedule, with free access to laboratory rodent chow and water. The animals were injected s.c. with 50 IU of equine chorionic gonadotropin (equine CG) (Teikoku Hormone, Tokyo, Japan) at 0900 h at 25 days of age to collect preovulatory ovaries at 0900 h on day 27. Immediately after the animals had been decapitated, the ovaries were removed and minced, and an equal mass of tissue (50 mg wet weight) from each animal was washed with Ca^{2+} and Mg^{2+}-free phosphate buffer saline (CMF) and cultured in 0.25 ml of Dulbecco's Modified Eagle's Medium (DMEM)/Ham F-12 (phenol red-free) (Gibco BRL, Grand Island, NY) supplemented with 100 μg/ml of gentamycin. Between 0.5 and 24 h after addition of all reagents tested, 225 μl of the culture media was collected, 25 μl of 1N HCl was added and the mixture was stored frozen at −40°C until assay for histamine. To obtain luteinized ovaries, rats were injected with 25 IU human CG (human CG) (Teikoku Hormone) i.p. at 1700 on day 27 after equine CG injection on day 25. Luteinized ovarian cells, which were collected 3 days after human CG treatment, were prepared as previously reported (Asakai et al., 1993).

2.2. Histamine assay

The histamine content in the culture media was measured following the fluorometric method, slightly modified by Hirasawa et al. (1987), which was originally developed by Shore et al. (1959). Namely, samples were mixed with 250 μl of 0.8 N perchloric acid, allowed to stand in ice-water for 10 min and centrifuged at 5000 rpm for 15 min. The supernatants were transferred to large glass tubes and 63 μl of 5 N NaOH, 0.2 g of NaOH and 1.3 ml of *n*-butanol were added. The tube was then shaken for 3 min and centrifuged. The upper butanol phase was mixed with 1 ml of NaCl-saturated 0.1 N NaOH and centrifuged. This procedure was repeated once more. To aliquots of the butanol phase were added 3.8 ml of *n*-heptan and 0.9 ml of 0.1 N HCl, followed by mixing for 2 min and centrifugation. To the bottom aqueous phase was added 0.2 ml of 1N NaOH followed by mixing, 50 μl of 1% (w/v) *o*-phthalaldehyde was then added and mixed. One hundred μl of 3N HCl was then added after incubation with *o*-phthalaldehyde in ice-water for 5 min. Fluorescence readings were made using 1-cm quartz cells in a Hitachi spectrophotofluorometer (Excitation slit, 10 nm; Emission slit, 5 nm). The level of histamine was expressed as the percent increase in histamine release as compared to the value of the control (100%) which was spontaneous release in unstimulated ovaries.

2.3. Ovarian steroid assay

Progesterone and 17β-oestradiol levels in the culture media were determined by RIA with a specific antiserum against progesterone (Bioproducts, England) and ELISA assay (Assay Designs, MI., USA), respectively. The intra- and inter-assay coefficients of variation in each assay were smaller than 20%. Data are presented as means ± S.E.M. The significance of the differences was tested by analysis of variance with Bartlett's test followed by Student's *t*-test. Differences with $P < 0.05$ were considered significant.

2.4. Immunohistochemistry for histidine decarboxylase

Paraffin-embedded sections were prepared after the tissues were fixed in Bouin's fixative. To find the localization of histidine decarboxylase, sections were stained using a polyclonal rabbit antiserum against histidine decarboxylase (B260-1, Euro-diagnostica, Malmö, Sweden). Sections in which endogenous peroxidase activity was quenched by incubation with 0.3% H_2O_2 in methanol were incubated with 10% normal goat serum. Slides were incubated with the primary antiserum at room temperature for 4 h or at 4°C overnight. Subsequently, sections were incubated with 0.5 g/ml goat anti-rabbit IgG antibody conjugated with peroxidase for 1 h and then visualized with True Blue peroxidase substrate (Kirkegaard & Perry Lab. Maryland, USA). Some tissues were also incubated with 0.5 μg/ml biotinylated goat anti-rabbit secondary (ABC-peroxidase staining Kit; Vector Lab., CA) for 1 h followed by 30 min incubation with 2% avidin–peroxidase complex. Bound antibody was visualized with 3,3′-diaminobenzidine (DAB,

Sigma) and counterstained in 0.125% methyl green. Serial section of ovaries were exposed to anti-CD34 antibody (Pharmingen, San Diego, CA, USA) to detect endothelial cells. Mast cells were detected as previously described (Tamura et al., 1998).

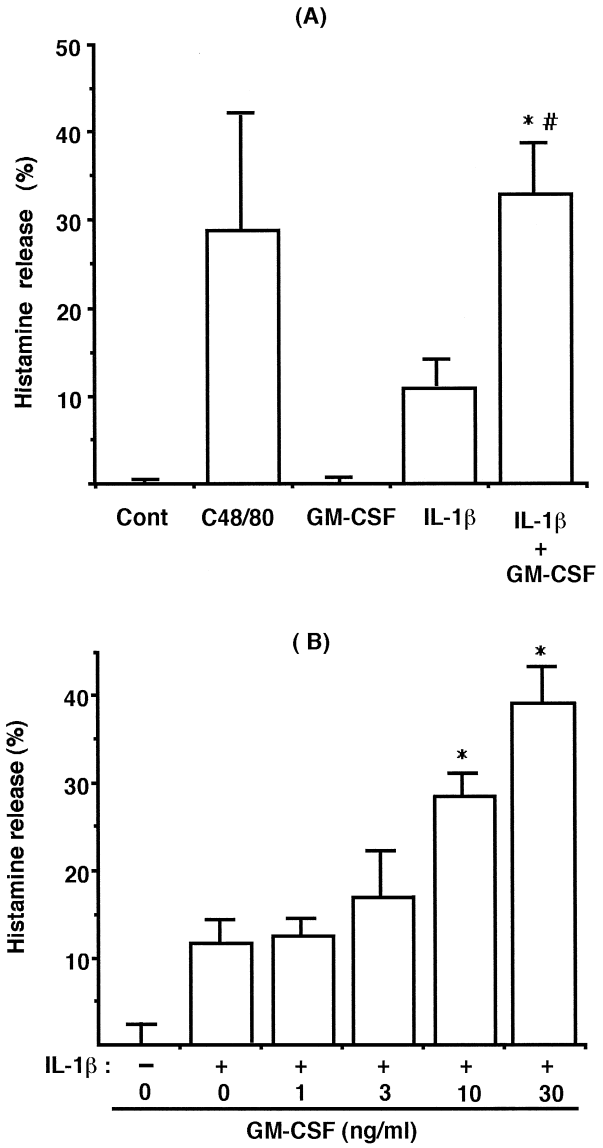

Fig. 1. Effects of GM-CSF and interleukin-1β on histamine secretion from cultured rat ovary. Immature rats were treated with equine CG as described in Section 2. (A) Ovarian tissues on the morning of the first pro-oestrus day were incubated for 3 h with compound 48/80 (C48/80) (10 μg/ml), GM-CSF (10 ng/ml) and/or interleukin-1β (10 ng/ml). Histamine released into the culture media was measured by a fluorometric assay. The control value was 38±5.6 ng per culture well. Each column shows the mean±S.E.M. of 8 cultures which were obtained from three identical experiments. $^{*}P < 0.05$; vs. interleukin-1β (IL-1β), $\#P < 0.05$; vs. control (Cont). (B) Dose-dependent effects of GM-CSF on ovarian histamine secretion in the presence of interleukin-1β Ovarian tissues were incubated with various doses of GM-CSF (1–30 ng/ml) for 3 h in the presence of interleukin-1β (10 ng/ml). Each column shows the mean±S.E.M. for 5 cultures which were obtained from two identical experiments. The control value was 41±4.8 ng per culture well. $^{*}P < 0.05$; vs. the interleukin-1β (IL-1β) only group without GM-CSF (0 ng/ml).

Table 1
Time course of the effect of GM-CSF and interleukin-1β on ovarian histamine secretion

	Incubation time (h)			
	1	3	6	12
Control	4.1±1.45	13.6±1.26	7.0±0.90	4.3±0.49
GM-CSF+ Interleukin-1β	6.5±0.48	18.3±0.65	10.0±0.78	5.2±0.30

Immature rats were treated with equine CG as described in Section 2 and ovarian tissues were excised on the morning of the first pro-oestrus day. Tissues were incubated with 30 ng/ml of GM-CSF and 10 ng/ml of interleukin-1β. Culture media were collected at 1, 3, 6, and 12 h of incubation. Results were expressed as rate of histamine production (ng) per hour. Each value shows the mean±S.E.M. for 4–12 cultures.

3. Results

3.1. Effects of GM-CSF and interleukin-1β on histamine secretion and steroidogenesis from preovulatory ovary

As shown in Fig. 1, we observed that 50 mg of ovarian tissues on the pro-oestrus day released approximately 40 ng (150 ng/ml) of histamine into the culture media after culture for 3 h. Compound 48/80, which induces a rapid release of histamine from mast cells, and interleukin-1β raised the levels of histamine by 28% and 11% as compared to the control, respectively, although the effects on histamine levels were not statistically significant. GM-CSF at concentrations between 1 and 30 ng/ml did not affect histamine secretion from the ovary (only the results for 10 ng/ml GM-CSF are shown in Fig. 1A). However, combined treatment with interleukin-1β and GM-CSF significantly enhanced the secretion of histamine from the ovary, as compared to control or the interleukin-1β only-treated group. To determine the dose–effect of GM-CSF in the presence of interleukin-1β (10 ng/ml), various doses of

Table 2
Effects of GM-CSF and interleukin-1β on the production of ovarian steroids in cultured preovulatory ovary

Treatment	Progesterone (ng/ml)	17β-oestradiol (ng/ml)
Control	16±2.8	22±3.4
Histamine	21±2.5	16±1.4
C 48/80	22±2.3	18±1.4
GM-CSF	18±4.3	18±1.9
Interleukin-1β	22±3.9	20±0.0
GM-CSF+Interleukin-1β	19±7.5	16±1.4

Ovarian tissues on the morning of the first pro-oestrus day were incubated for 6 h with histamine (3×10^{-6} M), compound 48/80 (C48/80) (10 μg/ml), GM-CSF (10 ng/ml) and/or interleukin-1β (10 ng/ml). Progesterone and 17β-oestradiol released into the culture media were measured by RIA and ELISA, respectively. Each value shows the mean ±S.E.M. for 3 cultures.

GM-CSF were added to the culture media (Fig. 1B). GM-CSF stimulated histamine secretion between 3 and 30 ng/ml GM-CSF in a dose-dependent manner. Histamine levels were significantly increased by treatment with 10 or 30 ng/ml of GM-CSF as compared with the interleukin-1β only-treated group. Time course studies (Table 1) revealed

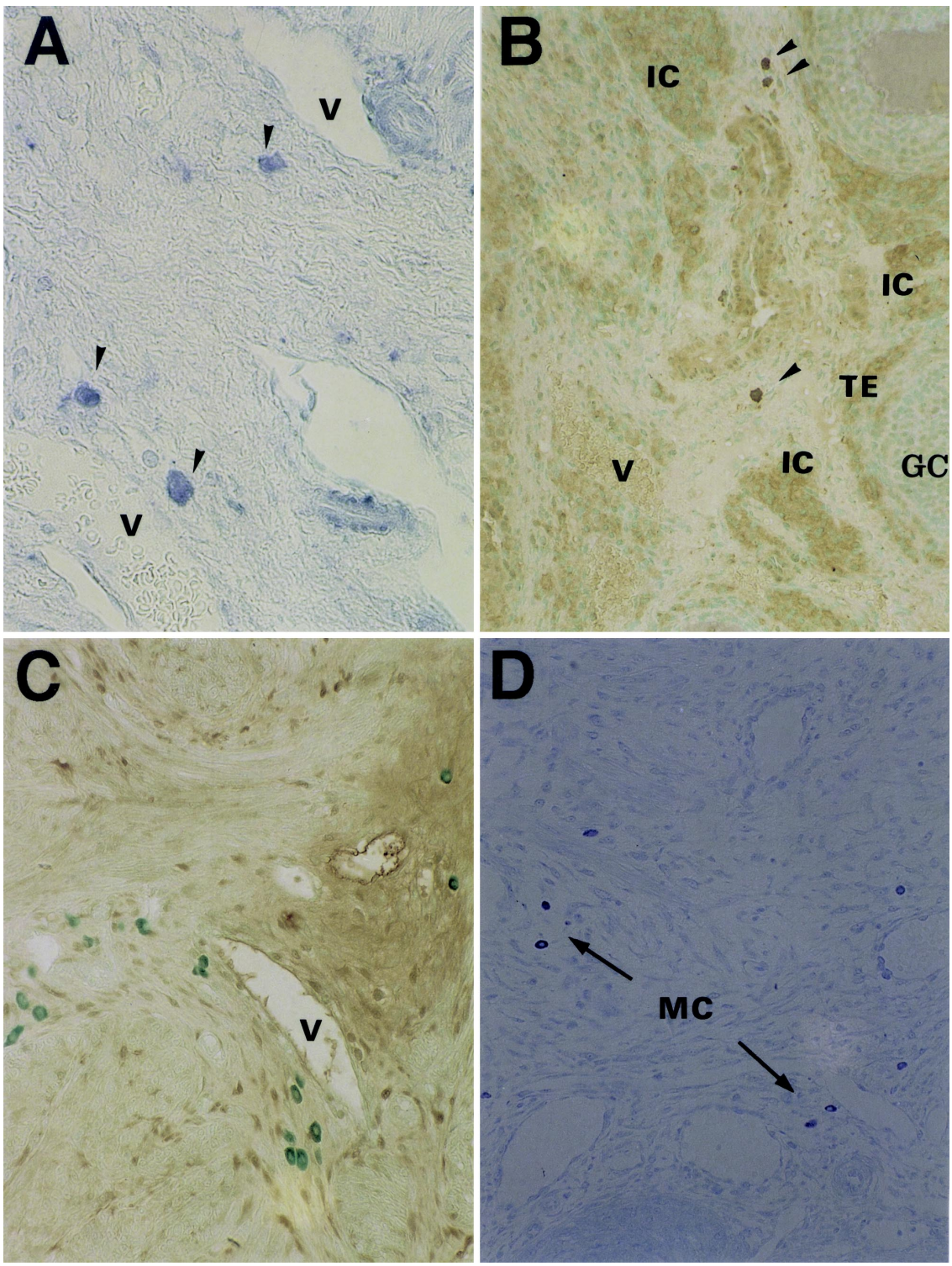

Fig. 2. Immunohistochemical localization of histidine decarboxylase in rat ovary. Ovaries were collected on the morning of the first pro-oestrus day and fixed with Bouin's fixative. (A) (×100) Staining with anti-histidine decarboxylase antibody. Positive staining was blue because of the staining of the enzyme with TrueBlue peroxidase substrate. (B) (×50) Staining with anti-histidine decarboxylase antibody. Positive staining was turned into brown because of the staining with 3,3′-diaminobenzidine. Sections were counterstained with methylgreen. Possible mast cells (arrowhead) are indicated. IC; interstitial gland cells, TE; theca externa cells, GC; granulosa cells; V; blood vessels. (C) (×50) Staining with anti-CD34 antibody. Positive staining was brown and sections were counterstained with methylgreen. (D) (×50) Staining with Toluidine blue dye. MC; mast cells.

that treatment with GM-CSF and interleukin-1β stimulated histamine release up to 12 h from 1 h of culture. The stimulatory effect of GM-CSF was maximal at 3 h of incubation in terms of histamine-producing capacity per unit time. To examine the effects of a combination of GM-CSF and interleukin-1β on steroidogenesis in preovulatory ovary, the levels of progesterone and 17β-oestradiol in the culture media were determined together with the effects of histamine and compound 48/80 (Table 2). However, no significant effects on either hormone were observed in any of the groups tested. Further, we observed that GM-CSF did not affect the basal or follicle stimulating hormone (FSH)-stimulated levels of 17β-oestradiol, progesterone, or inhibin in the culture media of granulosa cells (data not shown).

3.2. Localization of histidine decarboxylase in rat ovary

To determine whether rat ovary synthesizes histidine decarboxylase and what kinds of ovarian cells express histidine decarboxylase in preovulatory ovary, ovarian sections were stained with histidine decarboxylase antibody (Fig. 2A, B). Two different immunohistochemical procedures were used and Fig. 2A shows the results with secondary antibody conjugated with peroxidase and Fig. 2B, the results with biotin–avidin. Cells with an intense signal were large and round in shape, and were sparsely distributed around blood vessels in the ovarian stroma of the hilum. The signal for histidine decarboxylase was also observed in interstitial gland cells and theca externa cells. No immunostaining could be detected in theca interna and granulosa cells. To examine the cell types which have positive staining for histidine decarboxylase, endothelial cells (Fig. 2C) and mast cells (Fig. 2D) were detected with anti-CD34 antibody and with toluidine blue reagent, respectively. CD34-positive cells as indicators of endothelial cells were dispersed in theca-interstitial tissues and stroma as well as in the inside cells of blood vessels. A similar distribution pattern was observed using an anti-CD31 (PECAM-1) antibody (data not shown). Although histidine decarboxylase immunoreactivity was detected in many cells surrounding blood vessels, and since endothelial cells seem to have weak immunostaining for histidine decarboxylase, restricted co-localization of histidine decarboxylase and endothelial cells was not observed. In Fig. 2C, mast cells also seem to be strongly stained green with methylgreen, which was used for counterstaining. Toluidine blue-positive cells were detected around blood vessels in the ovarian stroma and showed a similar distribution of intense staining for histidine decarboxylase, indicating that ovarian mast cells produce histidine decarboxylase.

3.3. Effects of GM-CSF and interleukin-1β on steroidogenesis from luteinized rat ovary

The expression of GM-CSF and its receptor was observed in luteal tissues in rat ovary (Tamura et al., 1998). We thus examined the effects of GM-CSF on progesterone secretion, which is modulated by treatment with LH and interleukin-1β. Progesterone production was stimulated by the addition of LH between 1 and 10 ng/ml in a dose-dependent manner in the primary cell culture system. (Fig. 3A). Treatment with GM-CSF (10 ng/ml) or interleukin-1β (10 ng/ml) alone did not affect the levels of progesterone (Fig. 3B). Interleukin-1β between 1 and 30 ng/ml significantly inhibited the elevation of progesterone levels induced by LH, although treatment with GM-CSF had no effect (Table 3). As shown in Fig. 3B, the maximum decrease of progesterone levels by interleukin-1β was seen at 10 ng/ml of interleukin-1β, where control levels of progesterone were reached. The inhibitory effect of inter-

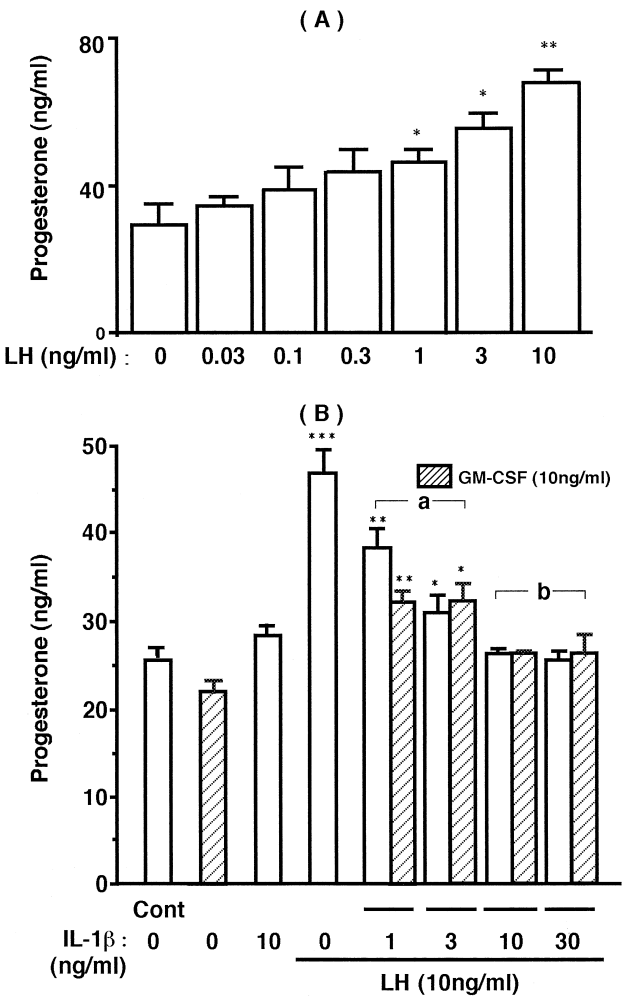

Fig. 3. Effects of GM-CSF and interleukin-1β on the production of progesterone in luteinized ovarian cells. Immature rats were treated with equine CG and human CG as described in Section 2. (A) Luteinized ovarian cells were cultured for 24 h in the presence of various doses of LH. Each value shows the mean ± S.E.M. for triplicate cultures. $^{*}P < 0.05$, $^{***}P < 0.001$; vs. Control (LH 0 ng/ml). (B) Luteinized ovarian cells were cultured for 24 h in the presence of LH (10 ng/ml), interleukin-1β and (1–30 ng/ml) and/or GM-CSF(10 ng/ml). Each value shows the mean ± S.E.M. for 6 cultures. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$; vs. Control (Cont) a, $P < 0.01$, b, $P < 0.001$; vs. LH (10 ng/ml). IL-1β; interleukin-1β.

Table 3
Effects of LH and GM-CSF on the production of progesterone in luteinized ovarian cells

Treatment	Progesterone (ng/ml)
Control	39 ± 2.7
LH	83 ± 4.7
GM-CSF (3)	35 ± 1.1
LH + GM-CSF (0.3)	88 ± 12.0
LH + GM-CSF (3)	75 ± 5.3
LH + GM-CSF (30)	72 ± 4.7

Luteinized ovarian cells were cultured for 24 h in the presence of LH (10 ng/ml) and/or GM-CSF. Each value shows the mean ± S.E.M. for 6 cultures obtained in the second series of identical experiments. Parenthesis shows the doses (ng/ml) of GM-CSF tested.

leukin-1β on LH-stimulated progesterone production was not influenced by GM-CSF (10 ng/ml) treatment, although the effect at a low dose of interleukin-1β (1 ng/ml) was slightly enhanced by GM-CSF treatment.

4. Discussion

In this study, we have demonstrated both the existence of histidine decarboxylase protein, a rate-limiting histamine-synthesizing enzyme in ovarian tissues, and the ability of GM-CSF to enhance the release of histamine, which may be a physiological regulator for ovarian function in rat ovary. The staining for histidine decarboxylase was mainly detected in large cells with granules near blood vessels, suggesting that the sources of histamine in the ovary are probably mast cells, although results obtained with histidine decarboxylase gene disrupted mice suggest that histidine decarboxylase is not only an enzyme for producing histamine (Ohtsu et al., 1998). Histidine decarboxylase was also localized to the interstitial gland and theca externa cells. It is well known that histamine release, which causes the enhancement of vascular permeability and contraction of blood vessels, is an essential reaction during early stages of allergic inflammation. In rat ovary, mast cells have been identified in the ovarian medulla and in the connective tissues of the hilum region in the ovary (Jones et al., 1980). Histamine from mast cells may be involved in the ovarian hyperaemia observed after the LH surge, because mast cells in the ovarian medulla degranulate on the pro-oestrus day (Krishna and Terranova, 1985). Piacsek and Huth (1971) reported that promethazine hydrochloride, an H_1 receptor antagonist, prevented the LH-induced increase in ovarian venous blood flow in rats. In addition to such possible involvement of histamine in ovarian vascular reactions, histamine might be a mediator of ovarian follicular contractility. In the human, histamine induces contraction of strips from the walls of ovarian follicles, and the contractile activity was greater in later follicular and ovulatory phases (Morikawa et al., 1981), suggesting that the increased release of ovarian histamine may contribute to the enhancement of contractility at the time of ovulation. Further, histamine can stimulate the proliferation of some types of cells, including smooth muscle cells (Maruno et al., 1995) and keratinocytes (Maurer et al., 1997), and mast cell degranulation increases the rate of angiogenesis in the chorioallantoic membrane (Rizzo and DeFouw, 1996). These findings might imply a role of histamine in the proliferation of ovarian cells and in angiogenesis related to the formation of a new corpus luteum as well as ovulation. GM-CSF and G-CSF induce histidine decarboxylase and ornithine decarboxylase in the spleen and bone marrow, but not in the liver and lung, with maximum effects at 4 h after their injection (Endo et al., 1992). GM-CSF and IL-3 enhance lipopolysaccharide-induced histamine production in bone marrow-derived macrophages (Takamatsu et al., 1996) and can potentiate the secretory response of human basophils (Radermecker et al., 1994; Columbo et al., 1995).

Interleukin-1β also stimulates histamine release from human basophils and mast cells (Subramanian and Bray, 1987) and immunoglobulin E (IgE)-mediated histamine release from human basophils (Massey et al., 1989). This cytokine can induce histamine release in rat hypothalamus in vivo (Niimi et al., 1994) and activate histidine decarboxylase in the bone marrow, spleen, lung and liver (Endo, 1989). In addition to these observations, our data showed that the rat ovary releases histamine in response to interleukin-1β, although the stimulation was not significant at 10 ng/ml of interleukin-1β and was detected only in the presence of GM-CSF at doses of more than 10 ng/ml. The present study also showed that GM-CSF stimulates interleukin-1β-induced histamine secretion whereas steroidogenesis in the preovulatory ovary was not influenced by treatment with GM-CSF and/or interleukin-1β. These data suggest that endogenous GM-CSF is probably not associated with the secretion of ovarian steroids, and that its stimulatory effect on histamine secretion is dissociated from steroidogenesis.

The doses of interleukin-1β and GM-CSF required to affect histamine release were somewhat higher than those reported to induce some other properties of these cytokines in vitro. This discrepancy may represent differences in the permeability of cytokines between tissue and cell preparations and in the affinity of binding sites for interleukin-1β and GM-CSF on different types of cells. Stimulation of the interleukin-1β production induced by LH in the preovulatory ovary may cause various inflammation-like responses which are thought to be essential for the rupture of Graafian follicles. Interleukin-1β-induced histamine release and the enhancement in histamine release in the presence of GM-CSF might be involved in such an inflammatory cascade in the process of ovulation.

In conclusion, if histamine is vital for ovarian physiology, GM-CSF released from the ovary may affect physiological functions of the ovary in an autocrine and/or paracrine manner by regulating histamine secretion and other immune responses in mast cells.

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