Interleukin 4 (IL-4) influences rat mast cell releasability

EWA BRZEZIŃSKA-BŁASZCZYK, ALICJA K. OLEJNIK

Department of Experimental Immunology, Medical University of Łódź, Poland

Abstract

There is growing evidence that cytokines may regulate biological functions of mature mast cells. In the following study we have investigated the capacity of IL-4 to induce direct mediator release from rat peritoneal mast cells as well as the action of this cytokine on mast cell secretory activity. We have determined that IL-4 does not activate rat mast cells to secretion of histamine and serotonin. We have also noticed that culture of these cells for 3 or 6 hours in the presence of IL-4 does not result in the IL-2 secretion. Yet, the results of our experiments have clearly shown that IL-4 treatment for 30 min causes the decrease of spontaneous histamine release from rat mast cells (up to 57.8% of maximal value at concentration of IL-4 100 ng/ml) and this decrease is statistically significant. Moreover, we have noticed that treatment of mast cells with IL-4 significantly inhibits compound 48/80-induced histamine release. IL-4 treatment does not change the reactivity of mast cells to ConA- and anti-IgE-stimulation. These results indicate that although IL-4 does not appear to be a direct stimulus for mediator release from mature rat mast cells, it may influence mast cell secretory activity.

Key words: *mast cells, interleukin 4, mast cell releasability*

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Introduction

Mast cells are widely distributed throughout the body in both connective tissue and at mucosal surface. They produce and release a spectrum of powerful mediators, including preformed mediators (e.g. amines, chemotactic peptides, proteoglycans, enzymes), newly synthesised mediators (e.g. arachidonic acid metabolites, nitric oxide) and cytokines [1, 2]. It is beyond doubt that mast cells play a pivotal role in immediate hypersensitivity reactions by virtue of the presence of high affinity receptors for IgE in their surface [1, 2]. Nowadays there is growing evidence that these cells are involved in other pathophysiological processes, such as chronic inflammation, tissue remodelling, wound repair, angiogenesis and fibrosis [3, 4]. Moreover, mast cells play an important role in homeostasis, normal host defence during innate immune response to bacterial infection and reactions to neoplasia [3, 5, 6]. Taking into account the significance of mast cells in the course of many physiological and pathological processes, it seems to be very important to recognise the factors that influence the biology and activity of these cells in tissues.

For over two decades it has been determined that cytokines play a crucial role in the regulation of various biological processes acting as chemical communicators between cells. Moreover, it is well established that cytokines affect the function of various cell populations [7]. It is now clear that most, if not all aspects of mast cells development, including growth, proliferation, and the differentiation/maturation, are regulated by cytokines [2]. There is also growing evidence that cytokines modulate the biology of mature tissue mast cells. It was documented that some cytokines influence the expression of mast cell surface receptors and molecules [8-10]. It was also established that many cytokines affect mast cell migration and adhesion acting not only as mast cells chemoattractants but also regulating the expression of adhesion molecules [11-14]. What is more, certain cytokines may control mast cell survival and apoptosis [15-18].

At present, several lines of evidence indicate that cytokines can also significantly influence the secretory activity of mast cells having either direct stimulating or regulatory effect. It has been shown that stem cell factor (SCF), nerve growth factor (NGF), tumor necrosis factor (TNF-α), macrophage

Correspondence: Ewa Brzezińska-Błaszczyk, PhD, Department of Experimental Immunology, Medical University of Łódź, Pomorska 251, 92-213 Łódź, Poland, tel. +48 42 675 73 06, e-mail: ewab@csk.am.lodz.pl

inflammatory protein (MIP-1α) and monocyte chemoattractant protein (MCP-1) can directly stimulate mast cells to release preformed and newly generated mediators [19-24]. Such cytokines as SCF, NGF and interleukin (IL)-3 were demonstrated to enhance mast cell responsiveness to stimulation [25-27], whereas treatment of these cells with transforming growth factor (TGF-β1), interferon (IFN)-γ or TNF-α causes the decrease of stimulated-mediator release [23, 26, 28-31]. In this report we have demonstrated that IL-4, one of numerous cytokines produced by activated mast cells, does not stimulate mast cells to secretion of mediators, although it influences mast cell releasability.

Materials and methods

Animals

The mast cells were obtained from peritoneal cavities of female albino Wistar rats weighting 200-250 g.

Mast cell isolation

The mast cells were obtained from the peritoneal cavity by lavage with 10 ml of the medium containing 137 mM NaCl, 2.7 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES buffer, and 5.6 mM glucose supplemented with 1 mg/ml bovine serum albumin (BSA) (pH of the medium was adjusted to 6.9). The peritoneal cell suspension was washed twice by centrifugation (150 g, 5 min, 4°C). After being washed, the cells were suspended in 1 ml of the medium and layered onto a Percoll solution after the method of Rossow et al. [32]. After centrifugation at 225 g for 20 min at 4°C, the mast cells sedimented. Those on the bottom of the tube were washed twice by centrifugation at 150 g for 5 min. After being washed, the mast cells were counted and suspended in an appropriate volume of the medium to obtain mast cell concentration $4x10^5$ cells/ml. The rat peritoneal mast cells were prepared with purity ≥90%, as determined by metachromatic staining with 0.1% toluidine blue.

In vitro experiments on rat mast cells and histamine release assay

The cell suspensions were carefully divided into 90-µl aliquots and incubated for equilibration at 37°C for 5 min. After that, 10 µl of stimulating agent, i.e. IL-4 in appropriate concentration as specified in the results, compound 48/80 at final concentration 10 µg/ml, concanavalin A (ConA) at final concentration 100 µg/ml or anti-IgE at final concentration 0.1 µg/ml, was added. Incubation was carried out in a water bath with constant stirring for different periods of time, as stated in the results. In some experiments, the mast cells were preincubated with IL-4 in concentrations 1 ng/ml, 50 ng/ml or 100 ng/ml for 60 min (the control mast cells were preincubated at the same conditions but without IL-4) and, after washing with the medium, were challenged with compound 48/80 (in a concentration of 10 µg/ml for 10 min), with ConA (in a concentration of 100 µg/ml for 30 min) or with anti-IgE (in a concentration of 1 µg/ml for 20 min). Addition of 1.9 ml of cold medium stopped the reaction. Next, the cell suspensions were centrifuged (150 g, 5 min, 4°C) and the supernatants were decanted into other tubes for histamine determination. A total of 2 ml of distilled water was added to each tube with cell pellet. In each experiment appropriate controls for the determination of spontaneous histamine release in the absence of stimulating agent were included. The histamine content was determinated in both cell pellets (residual histamine) and supernatants (released histamine) by spectrofluorometric method by use of *o*-phthalaldehyde (OPT) [33]. Histamine release was expressed as a percentage of the total cellular content of this amine after correction for the spontaneous release found in controls.

Serotonin release measurement

Purified mast cells were suspended in complete medium cDMEM (Dulbecco's modified Eagle's medium supplemented with 5% foetal calf serum (FCS), 2 mM L-glutamine and 40 µg/ml gentamycin) and cultured for 2 h at 37°C in the atmosphere of 5% CO_2 in air. One hour to the termination of the culture, 1 µCi/ml of [^{3}H]serotonin (5-[1,2-3H(N)]-hydroxytryptamine creatinine sulfate, sp. act. 27 Ci/mmol) that is selectively incorporated into MC granules, was added. After termination of the culture, the cells were washed twice with 2 ml of challenge medium (cDMEM with 10 mM HEPES) and resuspended in 2.5 ml of challenge medium. The cells (100 µl) were added in duplicate to 100 µl of challenge medium as a control, 100 µl of IL-4 (at final concentration 10 ng/ml or 100 ng/ml) or 100 µl of 0.05% Triton X-100 to lyse the cells. The cells were incubated for 30, 60 and 240 min at 37°C with 5% CO_2 in air, and next they were centrifuged at 350 g for 2 min. Then, 100 µl of the supernatant fraction was removed and added to 2 ml of scintillation cocktail. The samples were analysed for 1 min on a liquid scintillation counter. Percentage of specific release of [^{3}H]serotonin from mast cells was assessed as [(a-b)/(c-b)]x100 where a-cpm for IL-4 treated cells, b-cpm for control cells and c-cpm for lysed cells.

Measurement of IL-2 by ELISA

Purified mast cells were suspended in cDMEM and divided into 0.5 ml aliquots. Stimulating agent, i.e. IL-4 in two concentrations 1 ng/ml and 100 ng/ml, was added. Incubation was carried out at 37°C in the atmosphere of 5% CO_2 in air for 3 and 6 h. After termination of the culture, the cells were centrifuged at 150 g for 5 min. Supernatant fractions were collected and stored at -20°C until assayed for IL-2.

The IL-2 content in samples was quantitated with a commercial ELISA Set according to the manufacturer's protocol. Plates were read at 490 nm by ELISA reader sponsored by the Foundation for Polish Science.

Reagents

The sources of reagents were as follows: NaCl, KCl, $CaCl_2$, $MgCl_2$, glucose, *N-2*-hydroxyethylpiperazine-*N'*-ethanesulphonic acid (HEPES), ConA, compound 48/80, BSA, OPT, Triton X-100, Tween 20, toluidine blue, carbonate buffer were obtained from Sigma Chemical Company, Percoll was obtained from Pharmacia, mouse anti-rat IgE and recombinant rat interleukin 4 (rrIL-4) from R&D Systems, DMEM, FCS, gentamycin, and L-glutamine were obtained from Life Technologies, 5-[1,2-3H(N)]-hydroxytryptamine creatinine sulfate was obtained from NEN, and scintillation cocktail from Aqualuma Plus, Lumac LSC BV. OptEIA Rat IL-2 Set and Assay Diluent were obtained from Pharmingen. This ELISA Set include: anti-rat IL-2 polyclonal antibody, biotinylated anti-rat IL-2 monoclonal antibody, avidin-horseradish peroxidase conjugate, standards - recombinant rat IL-2.

Statistical analysis

Statistical parameters included mean value, standard error of the mean (SEM) and Student's test for "small groups". Values of $P < 0.05$ were considered as statistically significant.

Results

The ability of IL-4 to induce histamine secretion from rat peritoneal mast cells is shown in Figure 1. We have observed that this cytokine, in any concentration and any incubation time used, did not cause release of histamine from rat mast cells. Unexpectedly, we have noticed that IL-4 treatment may result in decrease of histamine secretion compared to histamine secretion from untreated mast cells. At the same time rat mast cells were activated and released histamine to the challenge with compound 48/80 (at the concentration 10 μg/ml), ConA (at the concentration 100 μg/ml) and anti-IgE (at the concentration 1 μg/ml) and percent of histamine release was up to 64.1 ± 2.0 (mean ± SEM), 24.1 ± 4.1, and 12.8 ± 3.0, respectively.

In the next series of experiments we have investigated the IL-4-induced serotonin release from rat mast cells. Mast cells were challenged with two concentrations of cytokine (10 ng/ml and 100 ng/ml) and the incubation time was 30, 60 and 120 min. At the same time control mast cells were incubated without IL-4 (spontaneous serotonin release). The results of these experiments are presented in Table 1. We have noticed that IL-4 stimulation did not activate rat mast cells to serotonin secretion in any conditions used.

We have also studied the effect of IL-4 treatment on the release of IL-2 from rat mast cells. Mast cells were cultured in the presence of IL-4 in the concentrations 1 ng/ml or 100 ng/ml for 3 and 6 h, and the cell free supernatants were assayed for the presence of IL-2. We have stated that in our experimental conditions IL-4 did not stimulate IL-2 release from rat mast cells (data not shown).

Regarding our earlier observations, we have investigated the influence of IL-4 on rat mast cell releasability. The cells

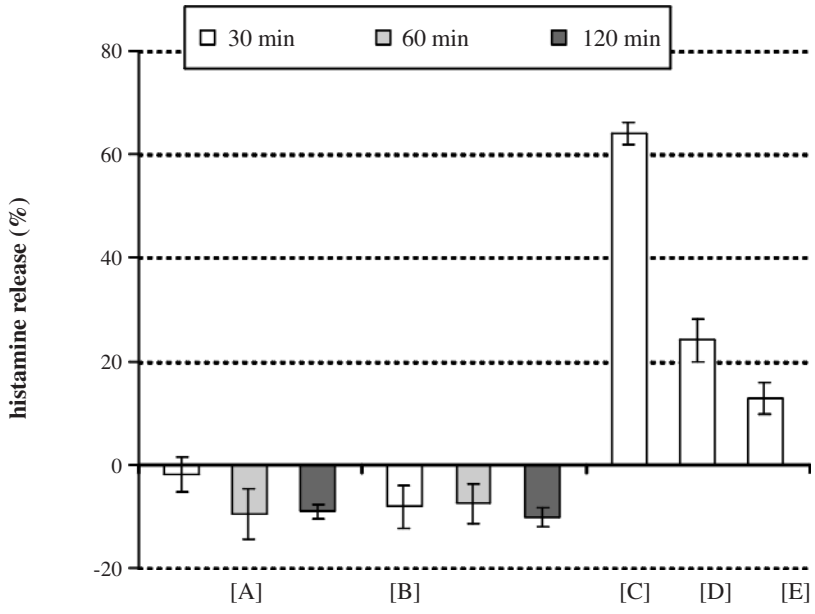

Fig. 1. Histamine release from rat mast cells induced by IL-4. IL-4 was used in two concentrations: 1 ng/ml [A] and 500 ng/ml [B]. Time of incubation: 30 min, 60 min or 120 min. For the comparison: [C] compound 48/80- (time of incubation – 10 min), [D] ConA- (time of incubation – 30 min), [E] anti-IgE- (time of incubation – 30 min) induced histamine release are shown. The results are the mean ± SEM of five experiments, with two replicates in each experiment

Table 1. The effect of IL-4-treatment on serotonin release from rat peritoneal mast cells. Mast cells were incubated with IL-4 at two different concentrations or buffer alone (spontaneous release). The results are mean ± SEM of 5 separate experiments with two replicates in each experiment

Time of incubation (min)	Spontaneous serotonin release (%) ± SEM [A]	Serotonin release (%) after incubation with two concentrations of IL-4 [B]		[B] – [A]	
		10 ng/ml	100 ng/ml	10 ng/ml	100 ng/ml
30	3.3 ± 0.3	3.8 ± 1.0	2.7 ± 0.2	0.5	-0.6
60	3.9 ± 0.5	4.2 ± 0.4	3.7 ± 0.4	0.4	-0.2
240	5.3 ± 0.4	5.1 ± 0.2	5.2 ± 0.2	-0.2	0.2

were incubated with different concentrations of IL-4 (from 1 ng/ml to 1000 ng/ml) for 30 min, and control mast cells were incubated without IL-4 at the same experimental conditions (maximal spontaneous histamine release). We have observed that the treatment of rat mast cells with 1 ng/ml, 500 ng/ml and 1000 ng/ml of IL-4 reduced the spontaneous histamine release up to 91.2%, 62.7% and 81.6% of maximal release, respectively, however the decreases were not statistically significant. The treatment of mast cells with IL-4 in concentrations 5 ng/ml, 10 ng/ml, 25 ng/ml, 50 ng/ml and 100 ng/ml resulted in statistically significant inhibition of spontaneous histamine secretion. The maximal decrease of spontaneous histamine secretion was up to 57.6% of maximal value at the concentration of IL-4 100 ng/ml (Fig. 2.).

To investigate the effect of IL-4 on rat mast cell responsiveness, the cells were preincubated with this cytokine and next were challenged with different stimuli. We have noticed that IL-4 treatment significantly inhibited compound 48/80-stimulated release of histamine, with the percent release decreasing to 69% of the control value (IL-4 concentration - 1 ng/ml), to 86% of the control value (IL-4 concentration - 50 ng/ml) and to 75% of the control value (IL-4 concentration - 100 ng/ml) (Fig. 3.). Pretreatment of mast cells with IL-4 in concentration 100 ng/ml resulted in decrease in ConA-dependent histamine release (up to 74% of the control value) however this decrease was not statistically significant (Fig. 4.). IL-4 treatment did not essentially influence mast cell responsiveness to anti-IgE stimulation as well (Fig. 5.).

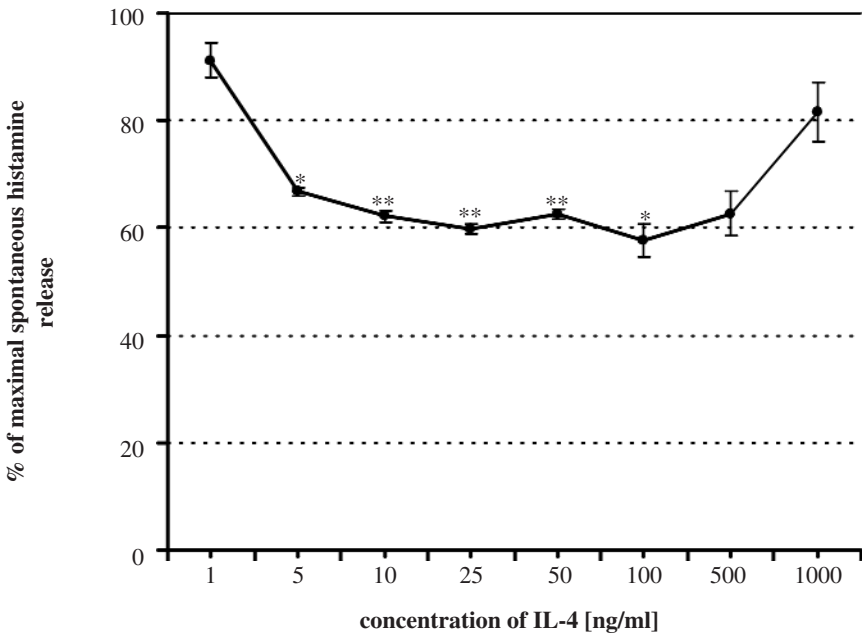

Fig. 2. Effect of IL-4-treatment on spontaneous histamine release from rat mast cells. Mast cells were incubated with different concentration of IL-4 or buffer alone (control mast cells) for 30 min. Each point represents the mean ± SEM of five experiments, with two replicates in each experiment. $^{*}p < 0.05$; $^{**}p < 0.02$, by comparison with buffer-treated cells; ♦% of maximal spontaneous histamine release found in control MC

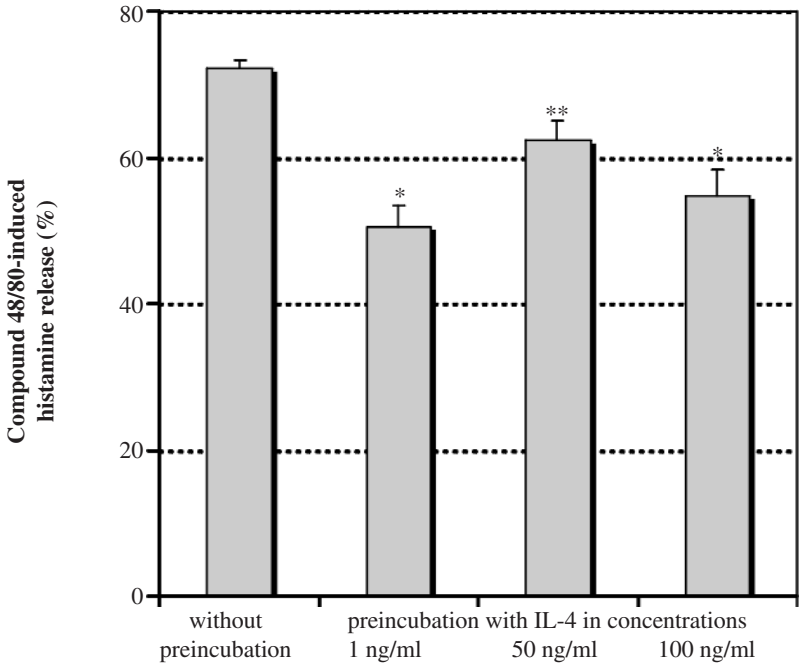

Fig. 3. Effect of pretreatment with IL-4 on mast cell reactivity to stimulation with compound 48/80. Mast cells were preincubated with IL-4 in concentrations 1 ng/ml, 50 ng/ml or 100 ng/ml (control mast cells were preincubated without IL-4) for 60 min, then washed, and challenged with compound 48/80 at a concentration of 10 μg/ml for 10 min. The results are the mean ± SEM of six experiments, with two replicates in each experiment. $^{*}p < 0.01$; $^{**}p < 0.02$, by comparison with buffer-treated cells

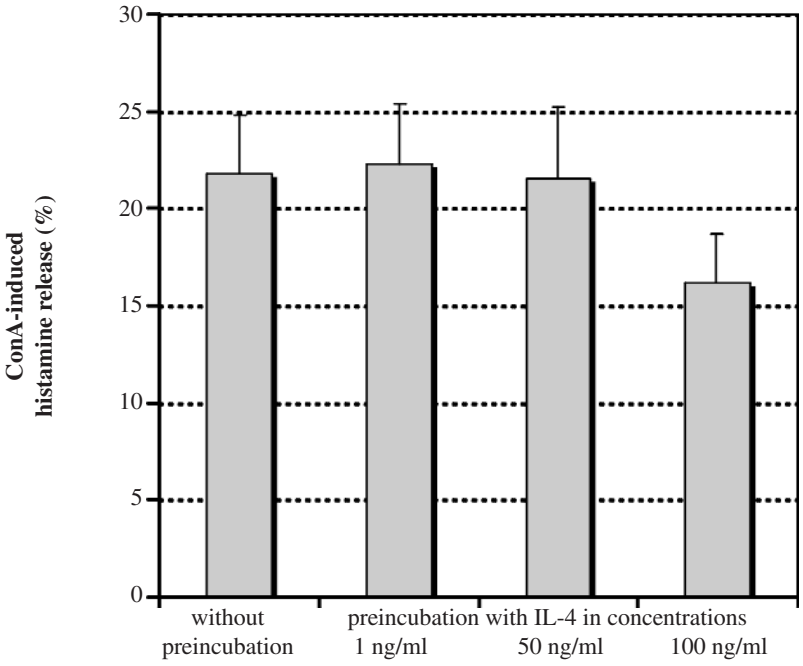

Fig. 4. Effect of pretreatment with IL-4 on mast cell reactivity to stimulation with ConA. Mast cells were preincubated with IL-4 in concentrations 1 ng/ml, 50 ng/ml or 100 ng/ml (control mast cells were preincubated without IL-4) for 60 min, then washed, and challenged with ConA at a concentration of 100 μg/ml for 30 min. The results are the mean ± SEM of six experiments, with two replicates in each experiment

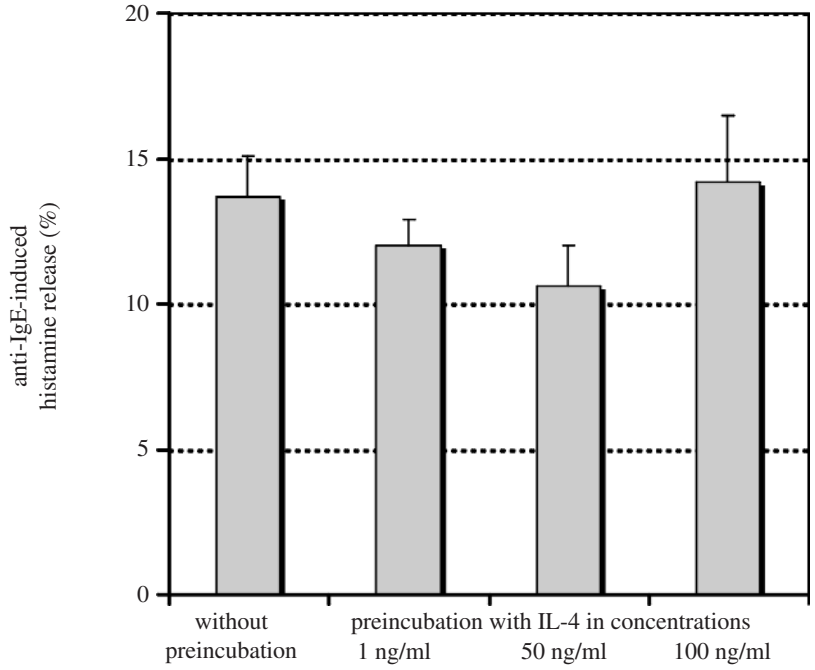

Fig. 5. Effect of pretreatment with IL-4 on mast cell reactivity to stimulation with anti-IgE. Mast cells were preincubated with IL-4 in concentrations 1 ng/ml, 50 ng/ml or 100 ng/ml (control mast cells were preincubated without IL-4) for 60 min, then washed, and challenged with anti-IgE at a concentration of 1 μg/ml for 20 min. The results are the mean ± SEM of six experiments, with two replicates in each experiment

Discussion

Various research groups have established that only some out of many cytokines stimulate mast cells to mediators release. It has been indicated that SCF induces histamine and prostaglandin D_2 (PGD_2) release from human cutaneous mast cells [34] and activates rat peritoneal mast cells to serotonin release [19]. It has also been documented that NGF stimulates rat mast cells to histamine and serotonin secretion. Alam et al. [24] have reported that mouse mast cells release histamine when incubated with MIP-1α and MCP-1. In our earlier reports we have noticed histamine release from human adenoidal and pulmonary mast cells and rat peritoneal mast cells to stimulation with TNF-α [22, 23]. In the present study we have established that IL-4 does not activate *in vitro* rat peritoneal mast cells to secretion of preformed mediators such as histamine and serotonin. Previously Coleman et al. [35] have noticed that IL-4 did not directly stimulate murine and rat mast cells to secretion of serotonin, and Bischoff et al. [36] have observed no mediator release from IL-4-stimulated human mast cells. We have also noticed that culture of these cells for 3 or 6 hours in the presence of IL-4 does not result in the IL-2 secretion. It should be pointed out, however, that IL-2 belongs to newly generated cytokines and we did not study the expression of mRNA encoding this cytokine. The results of our experiments have also clearly shown that IL-4, which by itself had no visible effect on rat mast cells, causes statistically significant decrease of spontaneous histamine release from rat mast cells. We have also established that the treatment of mast cells with IL-4 significantly inhibits compound 48/80-induced histamine secretion and slightly reduces ConA- and anti-IgE-induced release of histamine. Thus, these results may suggest that IL-4 downregulates the mast cell releasability. In our previous studies we have established that also TNF-α significantly reduced rat mast cell releasability [23, 30].

There is growing evidence that IL-4 strongly affects mast cell biology and functions. This cytokine was found, apart from other cytokines, to promote growth, proliferation and differentiation of rodent mast cells [37] and, in combination with SCF, to render mature mast cells to proliferation [36]. It was also established that this cytokine promotes chymase-positive mast cells from immature progenitors [38]. Although IL-4 is not a direct stimulus for mast cells mediator release, it influences the reactivity of these cells to stimulation. Coleman et al. [39] have reported that IL-4 enhances mast cell response to ionophore A23187 stimulation, Karimi et al. [27] have documented that preincubation of BMMC with IL-4,

together with SCF, causes the increase of secretion of β-heksozaminidase, leukotrien (LT)C_4 and PGD_2 to substance P (SP)-stimulation. Bischoff et al. [36] have shown that mast cells isolated from human intestinal tissue release more histamine, LTC_4 and IL-5 by IgE-receptor cross-linking when pretreated with IL-4. Holliday et al. [26] have reported that IL-4-treatment enhances IgE-dependent serotonin release from mouse peritoneal mast cells, and Ochi et al. [40] have noted higher anaphylactic histamine release from human mast cells after IL-4-treatment. It was also shown that IL-4 is a weak activator of IL-3 and IL-8 gene expression in HMC-1 cells [41] and up-regulates ionomycin-induced expression of mRNA encoding IL-4, granulocyte-macrophage colony stimulating factor (GM-CSF), IL-3 and IL-8 [35]. Moreover, IL-4 can inhibit nitric oxide production by rat peritoneal mast cells, resulting in increased IgE-dependent secretory function of rat mast cells [42]. It has been shown that this cytokine enhances the expression of some adhesion molecules such as ICAM-1 and LFA-1 [43], and regulates the adhesion of mast cells to extracellular matrix proteins [44] thus modulates the migration and cellular interaction between mast cells and other inflammatory cells. It was also documented that IL-4 influences mast cells survival and induced their apoptosis [15, 45].

It is thought that IL-4 may also influence mast cell functions indirectly. It has been documented that this cytokine induces the expression of FcεRI on mast cells [46], regulates B cell maturation to IgE-producing plasma cells [47] and stimulates T cell maturation toward the Th2 phenotype [48].

It is now well known that IL-4 plays an essential role in many immune and inflammatory responses. This cytokine is produced only by a small subset of cell populations, e.g. mast cells. IL-4 is localised to both subpopulations of mast cells, although predominantly in MC_{TC} [49]. It is well known that mast cells constitutively contain IL-4, which is stored in cytoplasmic granules and is secreted within seconds following IgE-dependent activation [50]. Moreover, it has been documented that mast cell stimulation induces an increasing mRNA level for this cytokine [51]. Taking into account that mast cells themselves are an important source of IL-4 it has been postulated that this cytokine may modulate mast cell biology in autocrine manner [39, 40]. Our observations that IL-4 decrease mast cell releasability are an additional proof that IL-4 is an essential autocrine factor influencing the functions of mast cells.

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