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Interferon-α/β inhibits IgE-dependent histamine release from rat mast cells

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SUMMARY

Although mast cells and interferons are both involved in numerous immune and inflammatory responses, little is known about how microenvironmental factors such as interferons (IFNs) influence mast cell function. To study this question, sensitized peritoneal mast cells (>98% purity) obtained from rats infected 4 weeks earlier with the parasite *Nippostrongylus brasiliensis* were preincubated for 24 hr with rat IFN-α/β in RPMI-1640, then stimulated to degranulate with worm antigens. In the absence of antigen, IFN-α/β had no noticeable effect on histamine release. However, in the presence of antigen, IFN-α/β (150–1500 U/ml) inhibited histamine release in a dose-dependent manner ($22{\cdot}2 \pm 7{\cdot}5\%$ to $56{\cdot}3 \pm 6{\cdot}9\%$, $n = 10$). This inhibitory effect was neither heat (56° for 1 hr) nor acid (pH 2 for 18 hr) labile, but was completely blocked by anti-IFN antibodies. In the presence of compound 48/80 (1 μg/ml) or substance P (5×10^{-5} M), IFN-α/β was ineffective at modulating histamine release. Histamine release induced by antigen in the presence of the membrane phospholipid phosphatidylserine (30 μg/ml) was inhibited by IFN in a dose-dependent manner, but maximal inhibition ($25{\cdot}3 \pm 2{\cdot}7\%$, $n = 10$) was reached at a lower concentration of IFN (750 U/ml) than when antigen was used alone. Therefore, rat IFN-α/β appears to inhibit histamine release from rat mast cells in a dose- and stimulus-dependent manner and may do so by reducing the fluidity of the cell membrane.

INTRODUCTION

Interferons (IFNs) are a family of anti-viral proteins that exert an array of immunoregulatory activities. They enhance binding to and lysis of tumour targets by NK cells (Mannering & Deloria, 1986), increase the phagocytic and cytotoxic functions of macrophages (Mannering & Deloria, 1986), regulate B-cell proliferation and Ig synthesis (Siegel, Le & Vilcek, 1986), inhibit the production (Knop, Taborski & DeMaeyer-Guignard, 1987) and activity (Sahasrabudhe, 1987) of T-suppressor cells, and control the expression of histocompatibility antigens on the surfaces of a range of cell types including IL-3-dependent mast cells in mice (Wong *et al.*, 1984). Of the three major classes of IFNs, IFN-α and IFN-β (type I IFNs) have been suggested to represent endogenous anti-inflammatory and anti-anaphylactic agents (Boraschi *et al.*, 1987). Indeed, type I IFNs inhibit the production of arachidonic acid metabolites (Boraschi, Censini & Tagliabue, 1984b; Boraschi *et al.*, 1984a, 1985, 1987), suppress endotoxin-mediated footpad swelling (Heremans *et al.*, 1987), and down-regulate Ia antigen expression induced by IFN-γ (Fertsch *et al.*, 1987).

However, IFN-α and IFN-β also demonstrate pro-inflammatory properties such as enhancing IgE-dependent secretion of histamine from human peripheral blood basophils (Ida *et al.*, 1977; Hernandez-Asensio *et al.*, 1979; Busse *et al.*, 1983). Moreover, because IFN-α exerts many opiate/endorphin-like effects, which can be blocked by the opiate antogonist, naloxone (Weigent & Blalock, 1987), and endorphins stimulate histamine secretion from mast cells (Shanahan *et al.*, 1984), it may be that IFN-α would also serve as a mast cell secretagogue.

Due to the nearly ubiquitous distribution of mast cells, their participation in many types of immune and inflammatory responses, and their numerous similarities with basophils, it is surprising that the influence of IFN on mast cells has not been studied. Therefore, to determine what effects IFN-α/β may have on IgE-dependent mast cell function, purified populations of rat peritoneal mast cells (PMC) sensitized with *Nippostrongylus brasiliensis*-specific IgE were preincubated for 24 hr with IFN and assayed for their ability to release histamine in response to stimulation with *N. brasiliensis* antigens. Interferon alone was not a secretagogue. However, rather than potentiating secretion, rat IFN-α/β inhibited mediator secretion in a dose-dependent manner in concentrations ranging from 150 to 1500

Abbreviations: DSCG, disodium cromoglycate; HTB, HEPES-buffered Tyrode's solution; IFN, interferon; PMC, peritoneal mast cells; PS, phosphatidylserine.

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U IFN/ml. The degree of inhibition appeared to be stimulus-dependent and was diminished by treatment of the cells with phosphatidylserine.

MATERIALS AND METHODS

Animals

Outbred Sprague–Dawley rats were purchased from Charles River Canada Inc., St Constant and were housed in filter-topped cages in a room where access was carefully regulated. Disposable outer garments, including footwear soaked in disinfectant, were required so that the risk of inadvertent infection to the animals, such as with pinworms, was minimized. Food and water were provided *ad libitum* and light cycles were maintained at 12 hr light/12 hr dark.

Nippostrongylus brasiliensis *infection*

Four weeks prior to mast cell isolation, adult (300–400 g) rats received 3000 third stage larvae of the intestinal parasite, *N. brasiliensis*, by a single subcutaneous injection into the scruff of the neck. This treatment results in sensitization of mast cells with anti-worm IgE (Befus *et al.*, 1982).

Cell isolation and culture

PMC were purified (>98% purity) from mixed peritoneal exudate cells by centrifugation through a two-step discontinuous gradient of sterile Percoll (Pharmacia Ltd, Dorval). They were then washed twice in sterile RPMI-1640 medium (Gibco, Grand Island, NY), which had an osmolality of 300 ± 8 mosm/kg, was buffered to pH 7·3 with 10 mM HEPES, and was supplemented with 10% fetal calf serum (FCS) and 1% penicillin/streptomycin (Gibco). Following resuspension in the same medium, PMC were distributed in 1-ml aliquots to sterile 15-ml conical centrifuge tubes (Falcon Plastics, Fisher Scientific, Edmonton) containing various amounts of rat IFN-α/β (Lee Biomolecular, San Diego, CA) and incubated at 37° for 24 hr.

Histamine release and assay

After 24 hr preincubation in the presence or absence of IFN, PMC were spun down, separated from supernatants, and resuspended to 4×10^5 cells/ml in Tyrode's solution buffered with 12 mM HEPES and containing 0·1% BSA (HTB), pH $7{\cdot}3 \pm 0{\cdot}1$ (Shanahan *et al.*, 1985). After equilibration at 37° for 5 min, 100-μl aliquots of PMC were distributed to 15-ml polypropylene centrifuge tubes containing releasing and release-modifying agents in 900 μl HTB (400 μl in substance P experiments). Histamine release was terminated after 10 min by centrifuging the tubes at 4°, after which the supernatant and cell pellet were separated. Both were brought to 3 ml with HTB, and the pellet fractions were placed in a boiling water bath for 10 min to release any remaining cell-associated histamine. After trichloroacetic acid precipitation of proteins, histamine levels were measured in both supernatant and pellet fractions by fluorimetric assay (Shore, Burkhalter & Cohn, 1959) using a Model LS-3B Perkin-Elmer fluorescence spectrometer. Histamine release was expressed as a percentage of the total cellular histamine content as calculated by the formula:

$$\frac{\text{histamine in supernatant}}{\text{histamine in supernatant and pellet combined}} \times 100.$$

The amount of histamine released in the absence of any stimulus (spontaneous release) was subtracted to give a value for specific histamine release. In all experiments, the spontaneous release was $\leqslant 5\%$. Percentage changes in histamine release induced by incubating PMC for 24 hr in IFN was calculated by the formula:

$$\frac{\begin{array}{c}\text{\% specific histamine release from PMC incubated in}\\ \text{the presence of IFN} - \text{\% specific histamine release}\\ \text{from PMC incubated in the absence of IFN}\end{array}}{\begin{array}{c}\text{\% specific histamine release from PMC incubated in}\\ \text{the absence of IFN}\end{array}} \times 100.$$

A negative value indicated that IFN treatment had an inhibitory effect on histamine release from PMC.

Cell viabilities

After Percoll purification and 24 hr preincubation with IFN, PMC viabilities were assessed by Trypan blue exclusion.

Chemicals

Rat IFN-α/β ($2{\cdot}7 \times 10^5$ U/mg) and rabbit anti-rat IFN-α/β (5×10^4 neutralizing units/ml) were purchased from Lee Biomolecular (San Diego, CA). According to the supplier, a neutralizing unit for their anti-IFN antibodies is an amount of antibody that will result in 50% neutralization of 10 U/ml rat interferon. Upon arrival, both IFN and anti-IFN were resuspended in 1 ml sterile distilled water, distributed aseptically in 6000-unit aliquots into autoclaved microcentrifuge tubes, and stored at 4° and −70°, respectively. Once opened, unused portions of aliquots of either IFN or anti-IFN were discarded. Substance P, compound 48/80 and phosphatidylserine were purchased from Sigma. Solutions containing substance P and phosphatidylserine were made fresh the day of each experiment. Phosphatidylserine was reconstituted as a suspension in HTB at 1 mg/ml after evaporating the chloroform in which the phopholipid was solubilized then pulverizing it in a ground glass homogenizer.

Antigen

The antigen used was a collection of soluble excretory and secretory products of adult *N. brasiliensis* worms prepared by incubating adults in PBS at 37° for 4 hr then removing the worms and their eggs (White & Pearce, 1982). Worms were counted and antigen concentration described as 'worm equivalents'/volume. Each week, a new batch of rats was infected and dose–response curves were generated to determine the lowest dose of the antigen preparation that gave maximal histamine release by PMC from those animals. In many instances, the sensitivity of the PMC varied so that antigen concentrations used in the IFN experiments varied from 1 to 60 worm equivalents/ml. Antigen did not induce histamine release from PMC of uninfected rats.

RESULTS

IFN inhibits antigen-induced histamine release

Preincubation of purified rat PMC for 24 hr at 37° with rat IFN-α/β reduced the magnitude of antigen-induced histamine secretion (Fig. 1). With increasing concentrations of IFN, between 150 and 1500 U/ml, inhibition of specific histamine release increased from $22{\cdot}2 \pm 7{\cdot}5\%$ at 150 U/ml, $34{\cdot}0 \pm 6{\cdot}8\%$ at 450 U/

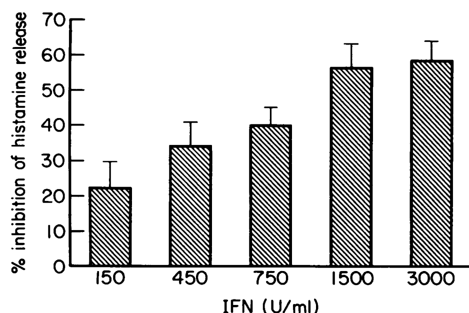

Figure 1. Inhibition by rat IFN-α/β of IgE-dependent histamine release from rat PMC. After 24 hr in culture in the absence of IFN, the specific release of histamine induced by worm antigen was $11 \pm 1{\cdot}2\%$. Under similar conditions, but in the presence of various concentrations of IFN, antigen-induced histamine release was inhibited in a dose-dependent manner at IFN concentrations up to 1500 U/ml. Each plot represents the mean and SEM for 10 experiments.

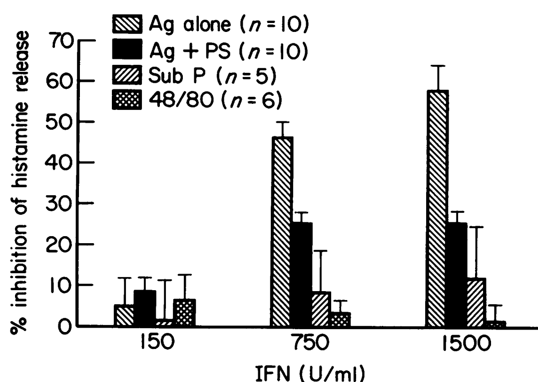

Figure 2. Inhibition by rat IFN-α/β of histamine release from rat PMC induced by various secretagogues. Specific histamine release from PMC cultured for 24 hr in the absence of IFN was $10{\cdot}1 \pm 0{\cdot}8\%$ for antigen (Ag), $34{\cdot}5 \pm 5{\cdot}0\%$ for antigen in the presence of phosphatidylserine (PS), $33{\cdot}4 \pm 4{\cdot}5\%$ for substance P, and $59{\cdot}5 \pm 4{\cdot}7\%$ for compound 48/80. Spontaneous release was less than 5%.

ml, $39{\cdot}9 \pm 5{\cdot}1\%$ at 750 U/ml, to $56{\cdot}3 \pm 6{\cdot}9\%$ at 1500 U/ml. There was no added inhibitory effect of IFN above 1500 U/ml because 3000 U/ml induced a $58{\cdot}4 \pm 5{\cdot}6\%$ inhibition of histamine release, similar to that of 1500 U/ml. Cells remained viable during the 24-hr culture period and no differences in viabilities between treatment groups were detected. In contrast to preincubation with IFN for 24 hr, preincubation of PMC with IFN for 8 hr did not induce inhibition of mediator secretion. Uninduced (spontaneous) release of histamine from PMC did not differ among the treatment groups; in all cases it was $<4\%$.

Specificity of the inhibitory effect of IFN for IgE-mediated histamine release

Histamine release stimulated by compound 48/80 (1 μg/ml), a pharmacological mast cell degranulator, was unaffected by preincubating PMC with concentrations of IFN up to 3000 U/ml (Fig. 2, data for 3000 U/ml not shown). Furthermore, over the same IFN concentration range, substance P-induced histamine release was also not reproducibly influenced (Fig. 2).

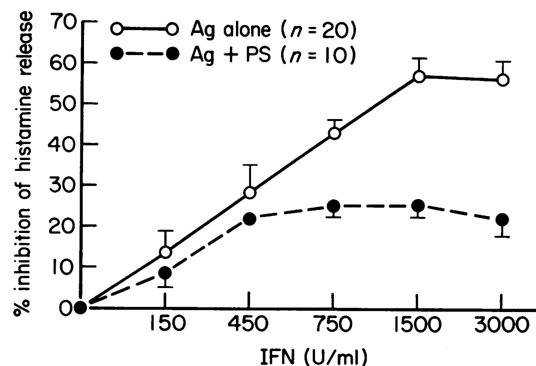

Figure 3. Influence of phosphatidylserine on the inhibitory effect of interferon on antigen-induced histamine release. Data from Figs 1 and 2 plus additional results were totalled to make this composite graph.

Although there appeared to be a trend toward greater inhibition at higher IFN concentrations, the standard errors were larger than the mean inhibition ($1{\cdot}4 \pm 9{\cdot}9\%$ at 150 U/ml, $8{\cdot}3 \pm 10{\cdot}3\%$ at 750 U/ml, and $11{\cdot}9 \pm 12{\cdot}8\%$ at 1500 U/ml). By comparison, IFN inhibited the release of histamine stimulated by antigen $4{\cdot}9 \pm 6{\cdot}9\%$ at 150 U/ml, $46{\cdot}3 \pm 3{\cdot}8\%$ at 750 U/ml, and $57{\cdot}9 \pm 6{\cdot}2\%$ at 1500 U/ml.

The membrane phospholipid, phosphatidylserine (PS, 30 μg/ml), which is not a mast cell secretagogue, caused no release of histamine from PMC, whether the mast cells were preincubated in the presence or absence of IFN. However, simultaneous addition of PS and antigen to preincubated PMC brought about a threefold or greater increase in mediator release above that induced by antigen alone. Nonetheless, despite such PS-elevated levels of mediator release, preincubating PMC for 24 hr at 37° with IFN also dampened histamine secretion in a dose-dependent manner as it did with antigen-mediated release (Fig. 2). PS-enhanced, antigen-induced release of histamine was inhibited $8{\cdot}5 \pm 3{\cdot}4\%$ (150 U/ml) to $25{\cdot}3 \pm 2{\cdot}7\%$ (750 U/ml). Inhibition with 1500 U/ml IFN was similar to that caused by 750 U/ml. Thus, IgE-mediated secretion, even after it is modified by a release potentiating agent such as PS, is affected to a larger extent by IFN than are 48/80 or substance P-induced release mechanisms.

In comparing mediator secretion induced by antigen alone or by antigen in combination with PS from IFN-treated PMC (Fig. 2), it appeared that PS may have helped over-ride some of the inhibitory effects of IFN. To examine this more carefully, all of the relevant data were collected and amalgamated into one composite graph (Fig. 3). Analysis of the data by two-way ANOVA revealed that PS significantly ($P < 0{\cdot}001$) dampened the inhibitory effect of IFN. The graph shows that at low concentrations of IFN ($\leqslant 450$ U/ml), PS exerts only a marginal influence at best, over the inhibitory action of IFN on antigen-mediated histamine secretion. However, at higher concentrations of IFN ($\geqslant 750$ U/ml), the additional inhibitory effects of IFN are completely negated by PS.

Neutralization of IFN

Rabbit anti-rat IFN-α/β antibodies completely eliminated the inhibitory influence of rat IFN-α/β on antigen-induced histamine release from rat PMC (Fig. 4). The step-wise manner in which this occurred with increasing amounts of neutralizing

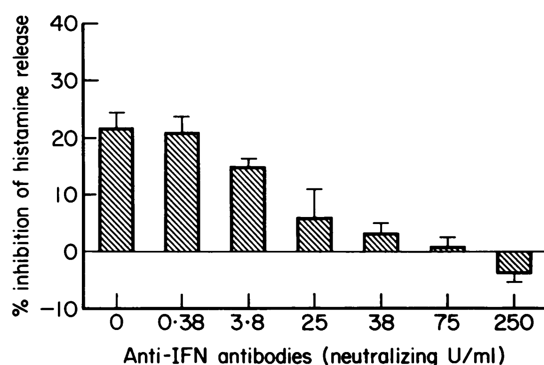

Figure 4. Neutralization by anti-IFN antibodies of the inhibitory effect of IFN on antigen-induced histamine release. PMC were incubated for 24 hr in the presence of 750 U/ml rat IFN-α/β that had been preincubated for 1 hr at 37° with various doses of anti-IFN antibodies. Histamine release was induced by *N. brasiliensis* antigen in the presence of phosphatidylserine ($n = 3$). In the absence of IFN, histamine release was $46·3 \pm 1·2\%$.

antibodies is consistent with the graded response PMC showed to decreasing IFN concentrations. The neutralizing antibodies alone did not stimulate histamine release and incubation of IFN in normal rabbit serum prior to use failed to diminish IFN's effects on histamine release.

Heat and pH

Essentially the same levels of histamine release in response to antigenic stimulation were achieved by PMC preincubated with IFN that had either been untreated, heated to 56° for 1 hr, or stored overnight at 4° at pH 2 prior to use. This is consistent with the nature of type I interferons.

DISCUSSION

Previous studies suggested that human peripheral blood basophils preincubated for 24 hr in the presence of IFN-α/β, IFN-α alone, or IFN-β alone responded to IgE-dependent stimulation with enhanced histamine release when compared to control cells incubated in the absence of IFN (Ida *et al.*, 1977; Hernandez-Asensio *et al.*, 1979; Busse *et al.*, 1983). Effective IFN concentrations included 80 IU/ml (Ida *et al.*, 1977), 800 IU/ml (Busse *et al.*, 1983), and 2500 IU/ml (Hernandez-Asensio *et al.*, 1979). In the present studies using rat PMC, IFN-α/β was also found to modulate IgE-dependent histamine release, but instead of augmenting degranulation, IFN inhibited it. The inhibitory effect required 24 hr to develop and increased with increasing concentrations of IFN over a range of 150 to 1500 U/ml (Fig. 1). That IFN-α/β apparently affects histamine secretion from human basophils and rat PMC in opposite ways, may reflect differences between the species and/or cell types in responsiveness to the protein. However, bearing in mind that highly purified (>98% pure) mast cell preparations were used in the present experiments, whereas in the basophil experiments either total leucocytes (Ida *et al.*, 1977; Hernandez-Asensio *et al.*, 1979) or basophil-containing mononuclear cells from Ficoll–Hypaque-separated whole blood were used (Busse *et al.*, 1983), it is also possible that when acting directly on mast cells or basophils, IFN inhibits secretion.

The secretion-inhibiting effects we found for IFN correlated well with the anti-viral properties reported by the supplier. Heat and low pH treatment, which were ineffective at eliminating the virus-inhibiting ability of rat IFN-α/β, were also unable to destroy IFN's inhibition of antigen-induced histamine release from PMC. Likewise, antibodies that neutralized IFN-induced inhibition of virus replication similarly neutralized IFN-induced inhibition of IgE-dependent histamine release from rat PMC. Thus, when taken together with the dose–response relationship between IFN and degree of inhibition of histamine release (Fig. 1), these results argue strongly that IFN-α/β acts directly on rat PMC to inhibit IgE-mediated histamine release.

It is interesting to note that Ribavirin, another anti-viral agent, has been shown to inhibit antigen-induced mediator release from murine bone marrow-derived mast cells (Marquardt, Gruber & Walker, 1987). As in the present experiments, prolonged (24 hr) incubation of mast cells and drug was required to produce the inhibition. Furthermore, there was a dose–response relationship between concentration of Ribavirin the mast cells were exposed to and degree of inhibition of mediator release. Hence, even though Ribavirin, a guanosine-like compound, and interferon, a protein, are structurally dissimilar, the mechanisms by which both compounds inhibit antigen-induced mediator release from mast cells may be similar and may be related to their anti-viral effects.

Because the anti-viral effects of IFN are dependent upon RNA and protein synthesis (reviewed by Mannering & Deloria, 1986), the mechanism by which IFN influences mast cell histamine release may also involve the production of new RNA and proteins. Indeed, the enhancement of histamine secretion in the human basophil system was prevented by inhibiting RNA synthesis with actinomycin D (Hernandez-Asensio *et al.*, 1979). However, it has also been shown that incubation of HeLa cells for 24 hr in 640 IU/ml human IFN-β results in increased rigidity of the plasmalemmal lipid bilayer (Pfeffer, Landsberger & Tamm, 1981), with a concomitant decrease in capping and internalization of cell surface receptors for concanavalin A (Pfeffer & Tamm, 1986). Similar alterations in membrane fluidity have also been found in mouse L-929 cells incubated with mouse IFN-β (Pfeffer *et al.*, 1981). An increase in membrane rigidity would help explain the results of the present experiments. IgE-mediated histamine release, which requires aggregation of cell membrane-bound IgE receptors and the formation of Ca^{2+} channels (Oliver *et al.*, 1988; Metzger *et al.*, 1986), would be expected to be more adversely affected by IFN than substance P- or compound 48/80-induced degranulation. This occurred in Fig. 2. Furthermore, one might predict that addition of the membrane phospholipid, phosphatidylserine, to the release reaction mixture would increase membrane fluidity and thereby diminish the inhibitory influence of IFN on antigen-induced histamine release. This also occurred in Fig. 3. Thus, experiments in progress to determine whether IFN alters membrane fluidity in rat PMC should shed some light on this area.

Disodium cromoglycate (DSCG) is another inhibitor of antigen-induced histamine release from mast cells (Pearce & Rafii-Tabar, 1983). Its mechanism of action is unknown but it is believed to involve 'stabilization' of the membrane. Intriguingly, the inhibitory influence of DSCG on histamine secretion from rat PMC is markedly reduced when PS is present at the time of activation and the dose of antigen used is maximal or near maximal. Thus, it may be that IFN and DSCG affect similar pathways in inhibiting histamine release from rat PMC.

Finally, Boraschi and co-workers showed that IFN-α and IFN-β inhibit production of prostaglandins E_2, I_2 and leukotriene C_4 by murine macrophages (Boraschi *et al.*, 1984a, b, 1985, 1987). This led them to propose that IFN-α and IFN-β may be endogenous anti-inflammatory and anti-anaphylactic agents that control reactions in which macrophages and arachidonic acid metabolites are importantly involved (Boraschi *et al.*, 1987). Our results suggest that IFN-α/β may have even more widespread application as an anti-phlogistic agent by also modulating IgE-dependent release of mediators from mast cells.

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