DOWNWARD REGULATION OF NEUTROPHIL INFILTRATION BY ENDOGENOUS HISTAMINE WITHOUT AFFECTING VASCULAR PERMEABILITY RESPONSES IN AIR-POUCH-TYPE CARRAGEENIN INFLAMMATION IN RATS

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Abstract—The role of histamine in neutrophil infiltration and vascular permeability response in carrageenin air pouch inflammation in rats was examined. Injection of carrageenin solution into an air pouch induced a gradual increase in histamine content in the pouch fluid and histidine decarboxylase activity of pouch wall tissues, with a maximum attained at 24 h. Local administration of the H2 antagonists cimetidine and famotidine, but not the H1 antagonist pyrilamine, induced an increase in neutrophil infiltration at 24 h. Both types of histamine antagonists failed to suppress the vascular permeability response. In addition, H2 antagonists attenuated the inhibitory effect of indomethacin on neutrophil infiltration without affecting the indomethacin-induced suppression of vascular permeability response. These results suggest that histamine produced in the inflammatory locus exerts a downward regulation of neutrophil infiltration through H2 receptors but does not play any significant role in the vascular permeability response. Furthermore, the inhibition by indomethacin of neutrophil infiltration might be ascribed to the increase in histamine level in the pouch fluid.

INTRODUCTION

In addition to proinflammatory actions, histamine exerts antiinflammatory actions in vivo and modulates functions of immune and inflammatory cells in...
vitro. For example, administration of histamine suppressed edema in adjuvant arthritis in rats (1) and reduced leukocyte infiltration in carrageenin-induced inflammation in rats (2). In the in vitro system, histamine inhibits production of interleukin-1 (3) and interleukin-2 (4), proliferation of T lymphocytes (5), enzyme release from neutrophils (6), and histamine release from basophils (7). However, it is unlikely that endogenous histamine released from mast cells exerts both the antiinflammatory actions and the proinflammatory actions at the same time because infiltration of immune and inflammatory cells into the inflammatory site generally occurs several hours later than mast cell degranulation.

In reference to this point, we reported that, in an allergic air-pouch-type inflammation in rats, histamine release was biphasic and the roles of histamine were apparently differed between the two phases (8, 9): In an anaphylaxis phase, histamine is released from mast cells immediately after the antigen challenge and the released histamine and serotonin are exclusively responsible for vascular permeability increase in the anaphylaxis phase (8). Histamine levels declined initially and then increased from 8 h reaching a maximum at 24 h (9). The latter increase in histamine level in the postanaphylaxis phase is caused by an induction of histidine decarboxylase (HDC) in the inflammatory tissues, and we hypothesized that the increased histamine in the postanaphylaxis phase modulates neutrophil infiltration through the histamine H2 receptor without affecting vascular permeability responses (9).

In the present work, by employing a nonallergic inflammation model, viz., the carrageenin air-pouch inflammation model in rats, we examined a role of histamine in neutrophil infiltration, since an increase in histamine levels in the inflammatory locus is reported in several carrageenin-induced inflammation models (10, 11). However, a role for histamine in such carrageenin-induced inflammation models remains to be elucidated. In this paper we describe that our hypothesis (9) also is applicable in the nonallergic inflammation model, namely, histamine produced in consequence of an increase in HDC activity participates in downward regulation of neutrophil infiltration through H2 receptors. Furthermore, inhibitory effects by the cyclooxygenase inhibitor indomethacin on neutrophil infiltration can be explained by an indomethacin-induced increase in histamine level in the inflammatory locus of carrageenin-induced inflammation, as demonstrated in the allergic air-pouch inflammation in rats (12).

MATERIALS AND METHODS

*Induction of Carrageenin Air-Pouch Inflammation.* Male Sprague-Dawley rats, specific pathogen-free, weighing 170–180 g (Charles River Japan, Inc., Kanagawa, Japan), were lightly anesthetized with diethylether and 8 ml of air was injected subcutaneously on the back to make an