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Atrial natriuretic peptide induces rat peritoneal mast cell activation by cGMP-independent and calcium uptake-dependent mechanism

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Abbreviations: ANP, atrial natriuretic peptide; cGMP, cyclic guanosine-3',5' monophosphate; TNF-α, tumor necrosis factor-α; RPMC, rat peritoneal mast cell; G proteins, heterodimeric GTP-binding proteins; cAMP, cyclic adenosine-3',5' monophosphate

Abstract

Atrial natriuretic peptide (ANP), a 28 amino acid basic polypeptide, is known to induce histamine release from human and rat mast cells *in vitro* and cause a wheel formation in rat skin. However, cellular events associated with histamine release are not clearly understood. In this study, we have examined the calcium flux and cGMP formation associated with histamine release in the ANP-treated mast cells. ANP, *in vitro*, induced mast cell degranulation and histamine release in a dose-dependent manner. ANP also induced an enhanced calcium uptake into cells and increased the cellular level of cGMP in mast cells. A high level of calcium in the media caused an inhibition of ANP-dependent histamine release but enhanced the level of intracellular cGMP of mast cells. ANP inducing a dose-dependent increase in vascular permeability of rat skin was confirmed by the extravasation of the circulating Evans blue. The results indicate ANP induced the histamine release and an increase in vascular permeability through mast cell degranulation in cGMP-independent and calcium uptake-dependent manner.

Keywords: ANP, mast cell, histamine, calcium, cGMP

Introduction

Mast cells are multifunctional effector cells of the immune system (Galli, 1990; Brody and Metcalfe 1998). These cells produce an array of vasoactive mediators and pro-inflammatory substances, like cytokines, histamine, protease, leukotrienes, tumor necrosis factor-α (TNF-α) and others (Welle, 1997; Shichijo *et al*., 1999; Brazis *et al*., 2000; Malaviya and Abraham, 2000; Yamashita *et al*., 2000). Among the preformed and newly synthesized inflammatory substances released upon degranulation of mast cells, histamine is the best characterized and most potent vasoactive mediator implicated in the anaphylaxis (Petersen *et al*., 1996). A general class of histamine secretagogues is compounds characterized by a net positive charge. In this category, the members of peptides containing one or more basic amino acids are polymixin B, bradykinin, substance P, C3a and C5a, somatostatin, neurotensin, protamine, and mellitin (el-Lati *et al*., 1994; Patella *et al*., 1997; Miller *et al*., 1998; Nemeth *et al*., 1998; Sugimoto *et al*., 1998; Furutani *et al*., 1999).

Mast cell activation can be produced by immunological stimuli which cross-link Fcε receptors, and by other agents such as anaphylatoxins and secretagogues. Some other drugs such as codeine, morphine and synthetic ACTH have also been found to act on mast cells direcly. The common feature in each case is the influx of calcium ions into the mast cell, which is crucial for degranulation. Microtubule formation and movement of the granule into the cell membrane lead to fusion of the granule with the plasma membrane, and the release of performed granule-associated mediators. Change in the plasma membrane associated with activation of phospholipase A_2 results in a release of arachidonic acid which is quickly converted into prostaglandins (PGD_2) and thromboxanes by the cyclooxygenase pathway and leukotrienes (LTC_4, LTD_4 and chemotactic LTB_4) by the lipoxygenase pathway (Roitt *et al*., 1998).

Recently atrial natriuretic peptide (ANP) has been shown to release histamine from peritoneal mast cells and to increase dermal vascular permeability in rats (Opgenorth *et al*., 1990). ANP is a 28 amino acid peptide hormone with vasodilator, natriuretic and diuretic properties (Stein and Levin, 1998). In this study, the signal mediator(s) during the ANP-induced histamine release from the mast cells was examined in an effort to better understand a possible mechanism of ANP-induced mast cell activation.

Materials and Methods

Materials

HEPES, bovine serum albumin (BSA), Hank's balanced salt solution (HBSS), and Evans blue dye were purchased from Sigma Chemical Co. (MO, USA). ANP was purchased from Peninsula (CA, USA). Percoll solution was purchased from Pharmacia (Uppsala, Sweden) and radioisotope was purchased from the NEN™ Life Science Products, Inc. (MA, USA). Cyclic GMP antibody was purchased from the Calbiochem-Novabiochem Corp. (CA, USA). Male Sprague-Dawley rats weighing 250-350 g were purchased from the Damool Science (Chungnam, Korea).

Preparation of peritoneal mast cell suspension of rat and microscopic observation

Rat peritoneal mast cells (RPMC) were isolated as previously described (Cochrane and Douglas, 1974). Briefly, rats were anesthetized by ether and injected with 10 ml of HEPES-Tyrode buffer containing 136 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 11 mM $NaHCO_3$, 0.6 mM NaH_2PO_4, 2.75 mM $MgCl_2$, 5.4 mM HEPES, 1.0 mg/ml bovine serum albumin, 1.0 mg/ml glucose, and 10 units/ml heparin into the peritoneal cavity, and the abdomen was gently massaged for about 90 s. The peritoneal cavity was opened, and the fluid was aspirated by a Pasterur pipette, and RPMCs were purified by using a percoll density gradient as described in detail elsewhere (Hachisuka *et al*., 1988). The purity and viability of cells were tested by toluidine blue staining and trypan blue exclusion (both > 95%), respectively (Mascotti *et al*., 2000). Purified mast cells (1×10^6 cells/ml) were resuspended in HEPES-Tyrode buffer. Mast cells were observed under phase contrast and photographed as described by Cochrane and Douglas (1974).

Assay of histamine release

Purified mast cell suspensions (200 μl; 1×10^6 cells/ml) were preincubated to 37 °C in HEPES-Tyrode buffer for 10 min and then incubated with the various concentrations of ANP (25 μl) for 20 min. The reaction was stopped by centrifugation at $150 \times g$ for 10 min and histamine content in the supernatant was measured by the radioenzymatic method of Harvima *et al.* (1988). Histamine release was calculated in percent of the total content of the cell suspension and corrected for spontaneous release occurring in the absence of ANP. Total histamine content was determined by 10 min boiling of aliquots of mast cells from the same animals in each experiment.

Measurement of ^{45}Ca uptake

The calcium uptake of mast cells was measured according to the method of Foreman (1977). Purified mast cells were resuspended in HEPES-Tyrode buffer containing ^{45}Ca (1.5 μCi/ml; 1 Ci = 3.7×10^{10} Bq), and incubated for 10 min at 4°C. Mast cell suspensions (200 μl; 1×10^5 cells/ml) were preincubated for 10 min at 37°C and then incubated with the various concentrations of ANP. The reaction was stopped by addition of 10 mM lanthanium chloride and the cells were washed 3 times by centrifugation at 4°C for 10 min. Mast cells in the pellet were disrupted with 10% Triton X-100 by vigorous shaking. Radioactivity of the solution was measured in a scintillation β-counter.

Measurement of cGMP level

The cyclic guanosine-3',5' monophosphate (cGMP) level was measured according to the method of Leithman *et al.* (1988). Briefly, mast cell suspensions (1×10^6 cells/ml) were added with an equivalent volume (200 μl) of prewarmed HEPES-tyrode buffer containing the drug in Eppendorf tube. The reaction was allowed to proceed for discrete time intervals, terminated by centrifugation, and added with sodium acetic buffer (250 μl). The mixture was vortexed vigorously and then snap frozen in liquid nitrogen. The sample was later thawed and vortexed, the debris was sedimented in a centrifuge ($400 \times g$ at 4°C, for 10 min). The cGMP level of supernatant was concentrated by water-saturated ether and determined by radioimmunoassay.

In vivo extravasation assay

Evans blue dye was prepared as a 1% solution (wt/vol) in sterile saline. Test compounds were prepared in saline to pH 7.4. Male Sprague-Dawley rats were used in these experiments. Rats were first anesthetized with ether, back skin hair was shaved, and rats were injected intradermally with 50 μl per site of the various concentrations of ANP. After 10 min, 1% Evans blue dye solution injected intravenously under ether anesthesia. After 30 min, rats were killed and punch biopsies were obtained, minced, and extracted with hot formamide (80°C, for 3 h) (Dombrowicz *et al*., 1997). Pooled samples from tissue sites were centrifuged and absorbance at 610 nm was measured. A_{610} values were converted to micrograms of Evans blue dye based on a standard curve of dilutions of Evans blue in formamide.

Statistical analysis

Data on the amount of histamine, calcium, cGMP, and Evans blue dye were represented as the mean (± SEM) in different experiments. Student's *t*-test was used to make a statistical comparison between the groups. Results with $P < 0.05$ were considered statistically significant.

Results

Atrial natriuretic peptide (ANP) induced the degranulation of rat peritoneal mast cells. The mast cell in HEPES-Tyrode buffered solution showed clear, smooth outline, spheroidal shape and contained many retractile

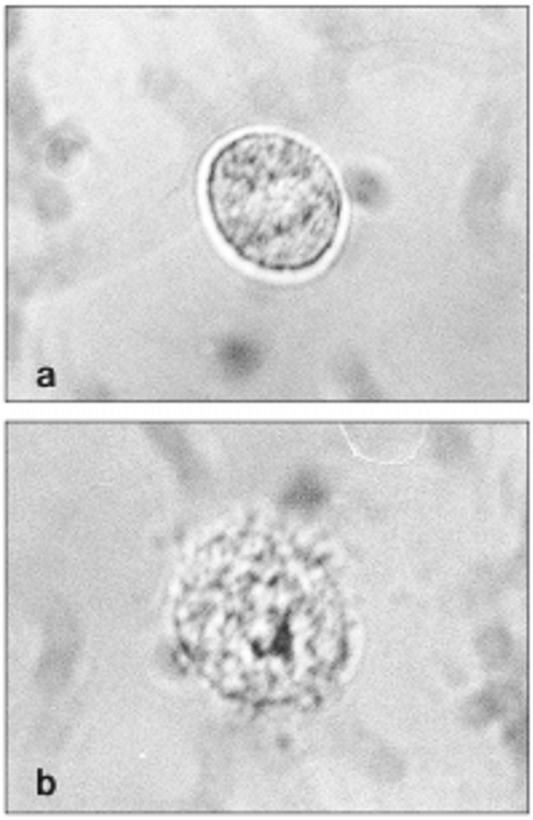

Figure 1. Light micrographs of rat peritoneal mast cells with HEPES-buffered solution (a) or ANP (b). Normal mast cell in HEPES-buffered solution is generally round or oval in shape with many cytoplasmic granules and smooth outline. Mast cell treated with 1×10^{-4} M ANP showed swelling, many vacuoles, irregular surface and extruded granules, indicating mast cell degranulation.

granules in its cytoplasm (Figure 1a). After the stimulation with 1×10^{-4} M of ANP for 5 min, rapid granule extrusion from the cell, disruption of the granular boundary, and swelling of cell shapes were observed indicating active degranulation of cell (Figure 1b).

Such ANP-induced histamine release was a dose-dependent: histamine release induced by 1×10^{-7}, 1×10^{-6}, 1×10^{-5}, and 1×10^{-4} M of ANP amounted to 6.31 ± 0.20, 20.24 ± 3.92, 31.75 ± 3.37 and 57.63 ± 6.92% respectively (Figure 2a). Results shown are the percentage of the total mast cell histamine released into the assay buffer.

ANP also induced calcium uptake into the mast cells in a dose-dependent manner (Figure 2b). Calcium uptake induced by 1×10^{-7}, 1×10^{-6}, 1×10^{-5}, and 1×10^{-4} M of ANP amounted to 107.40 ± 4.90, 220.60 ± 1.66, 233.70 ± 12.00 and 182.50 ± 2.91% respectively (the percentage of calcium uptake into the mast cells in HEPES-Tyrode buffered solution).

ANP increased the intracellular cyclic guanosine-3',5' monophosphate (cGMP) level of the mast cells, in a dose-dependent manner (Figure 2c). The amount of intracellular cGMP increased by 1×10^{-7}, 1×10^{-6}, 1×10^{-5}, and 1×10^{-4} M of ANP was to 622.80 ± 420.80, 2302.00 ± 212.30, 2380.00 ± 203.20 and 2551.00 ± 252.80% respectively. (the percentage of intracellular cGMP of the mast cells).

Figure 3 showed the effects of extracellular calcium on the ANP-induced histamine release and increase of intracellular cGMP level of the mast cells. The addition of calcium to 10 mM or higher concentration caused inhibition of the histamine release induced by ANP (Figure 3a). Histamine release induced by 1×10^{-4} M of ANP in the presence of 0, 10, 50 and 100 mM of calcium amounted to 65.83 ± 2.45, 45.71 ± 2.63, 31.90 ± 0.34 and 23.80 ± 0.29% respectively. However ANP increased the intracellular cGMP level, in the presence of an extracellular calcium in a dose-dependent manner (Figure 3b). The amount of intracellular cGMP increased by 1×10^{-4} M of ANP in the presence of 0, 10, 50 and 100 mM of calcium amounted to $119.00 \times 10^{-3} \pm 4.05$, $192.20 \times 10^{-3} \pm 21.58$, $295.50 \times 10^{-3} \pm 12.90$ and $545.90 \times 10^{-3} \pm 29.69$ pmol/tube respectively.

ANP induced the dermal vascular permeability, in a

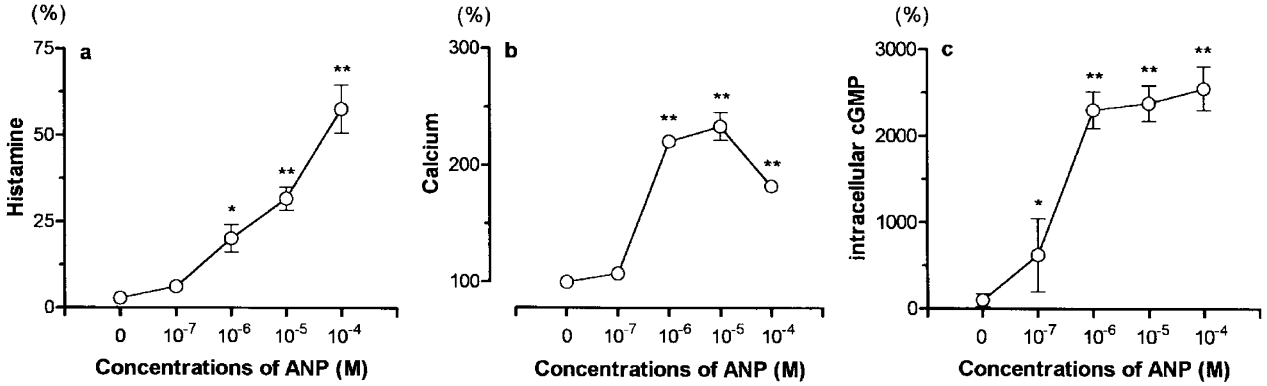

Figure 2. Effects of ANP on the rat mast cell activations. Mast cells were incubated with various concentraions of ANP for 20 min. ANP induced histamine release from mast cells (a), calcium uptake into the mast cells (b), and increase of intracellular cGMP level of the mast cells (c). Each point in the figures expresses the mean (± SEM). *P < 0.05, **P < 0.01 when compared with the control using a Students *t*-test.

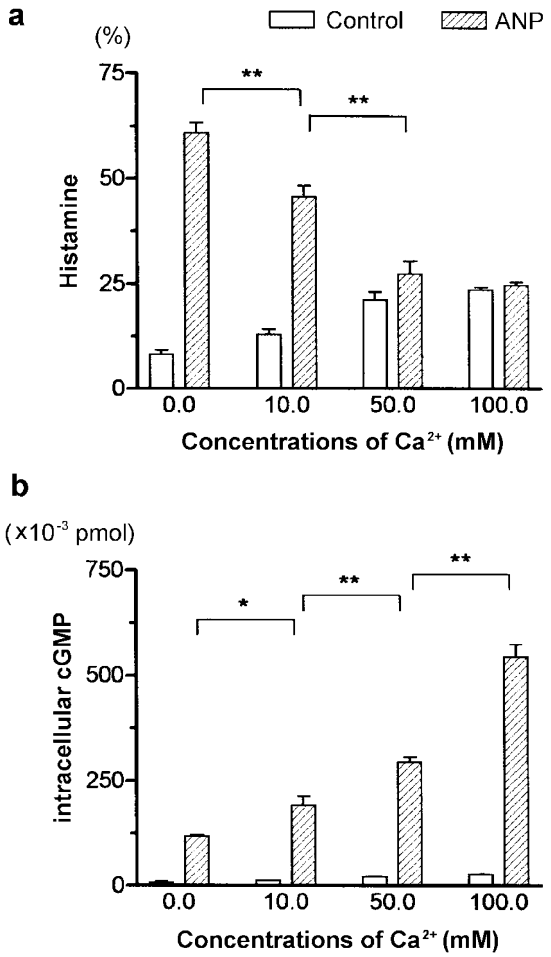

Figure 3. Effects of extracellular calcium on the histamine release (a) and intracellular cGMP level (b). Mast cells were stimulated without (control) or with 1×10^{-4} M of ANP. Each point in the figures expresses the mean (± SEM). *P < 0.05, **P < 0.01 when compared with the control using a Students *t*-test.

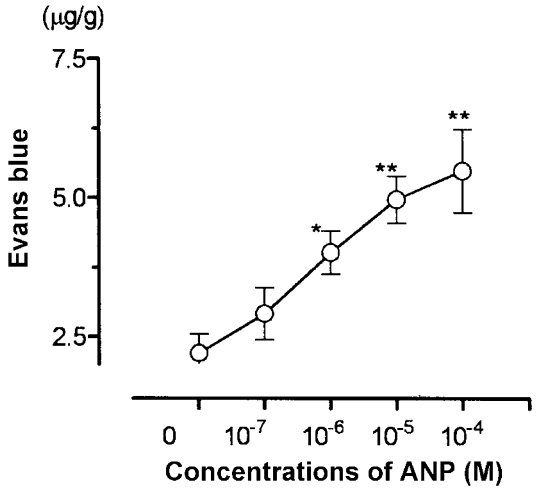

Figure 4. Effect of ANP on the dermal vascular permeability. Rats were injected *s.c.* with various amounts of ANP and 1% Evans' blue dye solution was injected *i.v.* after 10 min. These results are expressed as micrograms of Evans blue dye converted from A_{610} measurements of formamide-extracted tissue biopsies per tissue weight. Each point in the figure expresses the mean (± SEM). *P < 0.05, **P < 0.01 when compared with the control using a Students *t*-test.

dose-dependent fashion (Figure 4). The amount of Evans blue extracted by 1×10^{-7}, 1×10^{-6}, 1×10^{-5}, and 1×10^{-4} M of ANP was to 2.92 ± 1.15, 4.28 ± 1.19, 4.98 ± 1.04 and 5.50 ± 1.83 μg/g, respectivly (micrograms of Evans blue dye converted from A_{610} measurements of formamide-extracted tissue biopsies per tissue weight).

Discussion

The primary storage site of histamine in mammalian tissue is the mast cell (MacDonald, 1998). Virtually all of the histamine stored in mast cells is located in secretory granules. In the rat, these granules consist of a highly charged matrix of heparin and protein (Holgate, 2000) and contain serotonin in relatively high concentration (Lipnik-Stangelj *et al.*, 1999). There are a variety of agents known to induce mast cell degranulation, which are also commonly associated with anaphylactic shocks in the human and other mammals. It is commonly accepted that noncytotoxic secretagogue agents act on mast cells by binding to cell surface receptors and induce, through a variable sequence of steps, a change in free cytoplasmic calcium concentration, the signal that invokes the final common pathway culminating in exocytosis of the histamine-containing granules (Raison *et al.*, 1999).

In the mast cell exocytosis, heterodimeric GTP-binding proteins (G proteins) are involved in the stimulation of mast cell degranulation by basic peptides (Lorenz *et al.*, 1998; Aridor *et al.*, 1990). Thus, application of compound 48/80 and other cationic secretagogues transiently increase intracellular Ca^{2+} concentrations through G protein-mediated activation of phospholipase C. The peptide-induced mast cell degranulation assumes a direct interaction of peptides with G protein a subunits subsequent to their translocation across the plasma membrane (Lorenz *et al.* 1998). The calcium influx has two main results (Daniele, 1989). Firstly, there is an exocytosis of granule content with the release of preformed mediators, the major one being histamine. Secondly, there is the induction of synthesis of newly formed mediators from arachidonic acid leading to the production of prostaglandins and leukotrienes. Mast cell mediators include chemotactic and spasmogenic factors. Spasmogens produce the immediate response of bronchoconstriction and lead to increase small vessel permeability, edema and cell emigration. Chemotactic factors, and cytokines such as GM-CSF, IL-5 and TNF-α, lead to an active accumulation of neutrophils, basophils, eosinophils, macrophages and platelets. Production of a further set of inflammatory molecules by these infiltrating cells leads

to the late phase response and a chronic inflammatory response, typical of asthma (Roitt *et al*., 1998).

Basic peptides known to induce mast cell degranulation include a number of highly active histamine releasing agents. Atrial natriuretic peptide (ANP) is a good example of polybasic peptide, which was first discovered in atrial tissue and has potent diuretic, natriuretic and hypotensive activities (deBold, 1985). ANP is a 28 amino acid polypeptide containing a 17 amino acid ring closed by a disulfide bond between two cysteine residues (deBold, 1985; Stein and Levin, 1998). ANP contains 5 arginine residues interspersed along the entire length of the molecule, though two of the residues are adjacent in the 3 and 4 positions. This peptide also contains one anionic residue, aspartic acid, in the 13 position which negates the positive charge contributed by one of the arginine residues yielding a net positive charge of 4 at physiological pH (Opgenorth *et al*., 1990; Stein and Levin, 1998).

In present study, ANP was demonstrated to induce mast cell degranulation and to directly release histamine from rat peritoneal mast cells. A recent report demonstrated that ANP causes mast cell degranulation in rats *in vivo* and *in vitro* (Sharara *et al*., 1995). ANP dose-dependently induced histamine release at 10^{-7} M or higher concentrations, which is similar to the results of Opgenorth *et al*. (1990), and Yoshida *et al.* (1996). In previous reports, human natriuretic peptides ANP, brain natriuretic peptide (BNP) and c-typed natriuretic peptide (CNP) are known to induce histamine release from mast cells (Yoshida *et al*., 1996; de Plater *et al*., 1998).

In our study, we demonstrated the effects of extracellular calcium on the ANP-induced histamine release from the mast cells. The addition of calcium at a concentration of 10 mM or higher into the assay buffer dose-dependently inhibited the histamine release induced by ANP, which is similar to the results of Yoshida *et al*. (1996). The mechanism of histamine release by neuropeptides has been discussed by several workers, but the mechanism is still uncertain. Furthermore, the precise number of basic residues of these peptides to make them responsible for mast cell degranultion is not well known. In general, it is agreed that arginine residues are more effective than lysine residues and the spacing of basic residues is an important factor (Yoshida *et al*., 1996). In case of human natriuretic peptides, lysine and arginine are amino acids with one positive charge at physiological pH. The inhibition of ANP-induced histamine release due to extracellular calcium may be related to the suppression of ANP binding to negatively charged sites of the mast cell membrane.

In our study, ANP induced the extracellular calcium uptake into the mast cells. It has been reported that an increase in the intracellular calcium level is apparently a prerequisite for histamine release from mast cells (Tasaka, 1990a). It is also known that even in a calcium-free medium, histamine can be released from mast cells by some histamine releasers, such as compound 48/80 and substance P (Ichikawa *et al*., 1987; Tasaka, 1990b). In such cases, calcium is released from the intracellular calcium store, thus increasing the cytoplasmic calcium concentration. It is suspected that the mechanism by which extracellular calcium uptake induces histamine release by natriuretic peptides may be similar to that by compound 48/80 (Cabado *et al*., 1999; Ichigi, 1999).

It has been reported that secretion by mast cells is regulated by two classes of membrane receptors: those that activate adenylate cyclase to produce cyclic adenosine-3',5' monophosphate (cAMP); and those that stimulate guanylate cyclase to form cyclic guanosine-3',5' monophosphate (cGMP) (Daniele, 1989). The transient increase of cytoplasmic cAMP inhibits the release of histamine, slow-reacting substance of anaphylaxis, and other mediators. In contrast, formation of cGMP by stimulation of guanylate cyclase enhances mediator release. According to a current hypothesis, the balance between the inhibitory (cAMP) and excitatory (cGMP) messenger molecules regulate release of mediators (Daniele, 1989). It has been noted that ANP, BNP and CNP act *via* receptors with intrinsic guanylyl cyclase activity to stimulate the generation of cGMP as a second messenger (Fawkes *et al*., 1999). In present study, ANP dose-dependently enhances the intracellular cGMP level of mast cells. Also we demonstrated the effects of extracellular calcium on the ANP-induced increase of intracellular cGMP level of the mast cells. The addition of calcium at a concentration of 10 mM or higher into the assay buffer dose-dependently increased the intracellular cGMP level of mast cells induced by ANP.

Several tissue types have specific receptors for ANP, and the binding of ANP to its receptor leads to increase both intracellular cGMP and cGMP influx. ANP stimulates cGMP-PDE activity in the cells, most likely by increasing intracellular cGMP and independently of protein kinase G (Ahlström and Lamberg-Allardt, 2000). ANP stimulates calcium uptake in freshly isolated rabbit connecting tubules (CNT) and increased cytosolic cGMP without affecting calcium reabsorption in primary cultures of CNT (Hoenderop *et al*., 1999). Also it has been reported that ANP increases cellular cGMP content in cultured hepatocytes and decreases calcium, which seems to control calcium channels direct *via* a PT-sensitive G-protein and indirect by a cGMP-mediated mechanism (Pella, 1991).

In previous studies, several peptides such as substance P, C3a and C5a, somatostatin are known to promote histamine-dependent plasma extravasation when injected intracutaneously in rats (Pearce, 1986; Rivier *et al*., 1986; Kowalski *et al*., 1997). Also ANP has recently been shown to increase dermal vascular permeability of rat *in vivo* (Forman and Jordan, 1983; Opgenorth *et al*., 1990). We have shown that ANP produced a dose-

dependent increase in dermal permeability of rat *in vivo*, which is similar to the other reports (Forman and Jordan, 1983; Opgenorth *et al*., 1990).

Several mediators derived from mast cell, such as histamine and tumor necrosis factor (TNF-α), are known to increase vascular permeability. TNF-α is a cytokine that plays a key role in the induction of inflammation and many other biological responses (Jäättelä, 1991). Mast cells have been reported to synthesize TNF-α and to secrete TNF-α from both preformed and newly synthesized sources upon appropriate stimulation (Gordon and Galli, 1990). Previous studies have demonstrated that substance P stimulates histamine release and TNF-α production from uterine, brain and peritoneal mast cells (Cocchiara *et al*., 1995; Cocchiara *et al*., 1999a; Cocchiara *et al*., 1999b). Also TNF-α immunoreactivity of rat peritoneal mast cell (RPMC) granules decreases during early secretion induced by compound 48/80. The changes in the immunolocalization and/or density of TNF-α immunoreactivity occur very rapidly upon stimulation of compound 48/80 (Beil *et al*., 1996). In our study, ANP stimulates histamine release and dermal vascular permeability. Taken together, these findings suggest that ANP may be capable of stimulating TNF-α production from RPMC. Accordingly, it will be of interest to investigate ANP-induced TNF-α production from RPMC and the relationship of calcium or cGMP and TNF-α production.

In conclusion, ANP is capable of inducing histamine release and increasing vascular permeability through mast cell degranulation in cGMP-independent and calcium uptake-dependent manner.

Acknowledgments

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