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Nanomolar concentrations of neuropeptides induce histamine release from peritoneal mast cells of a substrain of Wistar rats

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Abstract

Substance P causes histamine release from rat peritoneal mast cells probably through direct activation of a specific G protein at micromolar concentrations. We found that peritoneal mast cells of a substrain of Wistar rats (Std:Wistar) responds to nanomolar concentrations of substance P by releasing histamine in a concentration-dependent manner. In addition, potent histamine release from peritoneal mast cells of the substrain rats was also induced by neurokinin A in a concentration-dependent fashion. Histamine release induced by low concentrations of substance P was significantly blocked by a tachykinin NK_1 receptor antagonist, CP-96345 [(2*S*,3*S*)-*cis*-2-(diphenylmethyl)-*N*-[(2-methoxyphenyl)-methyl]-1-azabicyclo[2.2.2]octan-3-amine dihydrochloride], whereas that induced by concentrations as high as 10 μM appeared resistant to the antagonist. The concentration-histamine release curve for neurokinin A was parallel-shifted to the right by the drug. A tachykinin NK_2 receptor antagonist, SR-48968 [(*S*)-*N*-methyl-*N*[4-(4-acetylamino-4-phenyl piperadino)-2-(3,4-dichlorophenyl)butyl]benzamide], did not influence release stimulated by substance P and neurokinin A. On the other hand, peritoneal mast cells of Sprague–Dawley and other Wistar rats did not respond to neurokinin A. At over 1 μM but not at nanomolar concentrations, substance P caused modest histamine release from peritoneal mast cells of these rats. The results suggest that neurokinin A and nanomolar, but not micromolar concentrations of substance P stimulate tachykinin NK_1 receptors on the peritoneal mast cells of Std:Wistar rat to release histamine.

Keywords: Substance P; Neurokinin A; Mast cell; Histamine release; Tachykinin NK_1 receptor; (Rat)

1. Introduction

Foreman et al. (1983) reported that intradermal injection of the neuropeptide, substance P, into human skin results in wheal and flare reaction which is reduced by prior treatment with a histamine H_1 receptor antagonist. In addition, micromolar concentrations of substance P also induce histamine release from skin mast cells but not from other organ mast cells of humans (Lowman et al., 1988). Large quantities of neuropeptides, including substance P, are located in the sensory nerve endings. Therefore, it has been considered that substance P-induced release of histamine is an important event in neurogenic inflammation.

Rat peritoneal mast cells have been widely used to investigate the mechanisms of substance P-induced histamine release from mast cells. Substance P causes degranulation of rat peritoneal mast cells possibly through direct activation of pertussis toxin-sensitive G proteins in the inner surface of the plasma membrane but not through activation of specific receptors such as tachykinin NK_1, NK_2 or NK_3 receptors (Mousli et al., 1990). This is because (1) high concentrations (micromolar range) of substance P are required to activate mast cells (Johnson and Erdös, 1973; Kitada et al., 1980; Erjavec et al., 1981; Fewtrell et al., 1982), (2) tachykinin NK_1 receptor antagonists with peptide structures also act as potent secretagogues (Mazurek et al., 1981; Fewtrell et al., 1982; Devillier et al., 1985, 1989) and (3) pretreatment with pertussis toxin potently inhibits histamine release (Mousli et al., 1989). Furthermore, the N-terminal domain (arginine and lysine in position 1 and 3, respectively) of substance P seems to stimulate the mast cells to release histamine (Mazurek et al., 1981; Fewtrell et al., 1982; Devillier et al., 1985, 1989), and the C-terminal domain apparently acts merely as a hydrophobic moiety for the release (Repke et al., 1987) although this domain is essential for tachykinin NK_1 receptor activation (Dion et al., 1987; Regoli et al.,

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1988). Neurokinin A, which has no arginine in the N-terminal domain, produces no histamine release from rat peritoneal mast cells (Devillier et al., 1985; Arock et al., 1989).

On the other hand, among several rat strains, Sprague–Dawley (Johnson and Erdös, 1973; Devillier et al., 1985, 1989; Repke et al., 1987; Arock et al., 1989) or Wistar (Mousli et al., 1989) have been extensively used to investigate the mechanisms of substance P-induced degranulation. Our laboratory uses Wistar rats bred by Japan SLC (Std:Wistar) to study anaphylactic histamine release (Nabe et al., 1992; Kohno et al., 1993; Kohno et al., 1994; Yamamura et al., 1994a). We found that low concentrations (nanomolar range) of not only substance P but also neurokinin A induce histamine release from peritoneal mast cells obtained from Std:Wistar rats. In the present study, we determined whether or not high sensitivity to these neuropeptides is a general phenomenon among Wistar strain rats. In addition, mechanisms of the release by nanomolar concentrations of substance P and neurokinin A were investigated using specific tachykinin NK_1, CP-96345 (Snider et al., 1991), and NK_2, SR-48968 (Emonds-Alt et al., 1992), receptor antagonists.

2. Materials and methods

2.1. Animals

Eight-week-old, male Wistar rats from several sources, and Sprague–Dawley rats were obtained as follows. Std:Wistar and Std:Wistar/ST (Japan SLC, Hamamatsu, Japan); Siz:Wistar (Shimizu Laboratory Supplies, Kyoto, Japan); Iar:Wistar Imamichi (Imamichi Institute for Animal Reproduction, Ibaraki, Japan); Sea:Wistar (Seac Yoshitomi, Fukuoka, Japan) and Slc:Sprague–Dawley (Japan SLC, Hamamatsu, Japan). The animals were housed in an air-conditioned room at a temperature of 23 ± 1°C and 60 ± 10% humidity with lights on from 8:00 AM to 8:00 PM for at least one week after purchase. They were fed a standard laboratory diet and given water ad libitum.

This animal study was approved by the Experimental Animal Research Committee at Kyoto Pharmaceutical University.

2.2. Reagents

Reagents and their sources were as follows: substance P (Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2) and neurokinin A (His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH_2) (Peptide Institute, Osaka, Japan), acetyl-[Arg^6, Sar^9, $Met(O_2)^{11}$]substance P-(6–11), bovine serum albumin (Cohn fraction V) and compound 48/80 (Sigma, St. Louis, MO, USA), CP-96345 (tachykinin NK_1 receptor antagonist, (2*S*,3*S*)-*cis*-2-(diphenylmethyl)-*N*-[(2-methoxyphenyl)-methyl]-1-azabicyclo[2.2.2]octan-3-amine dihydrochloride, supplied by Pfizer Inc., Groton, CT, USA), SR-48968 (tachykinin NK_2 receptor antagonist, (*S*)-*N*-methyl-*N*[4-(4-acetylamino-4-phenyl piperadino)-2-(3,4-dichlorophenyl)butyl]benzamide, supplied by Sanofi-Recherche, Montpellier, France), gelatin (Merck, Darmstadt, Germany) and heparin (Novo-Nordisk, Gentofte, Denmark).

2.3. Harvest and purification of peritoneal mast cells

Peritoneal mast cells were harvested and purified as described (Kohno et al., 1994). Following anaesthesia by inhalation of diethyl ether, rats were killed by stunning and exsanguinated through an incision in the carotid artery. They were then injected i.p. with 100 ml/kg of Ca^{2+}-free mast cell medium (composition: NaCl 150 mM, KCl 3.7 mM, Na_2HPO_4 3.0 mM, KH_2PO_4 3.5 mM and glucose 6.0 mM) containing 0.1% bovine serum albumin, 0.1% gelatin and 10 U/ml heparin. After gentle abdominal

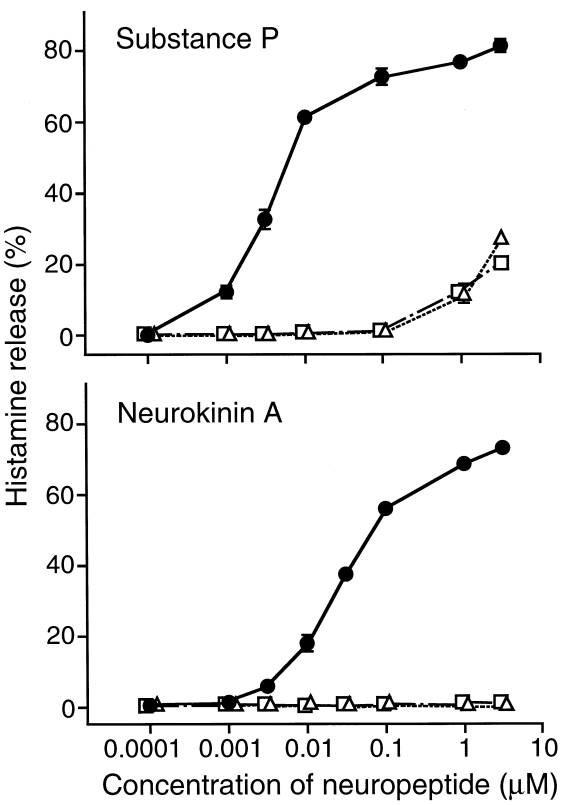

Fig. 1. Substance P- and neurokinin A-induced histamine release from peritoneal mast cells of Std:Wistar (●), Std:Wistar/ST (△) and Slc:Sprague–Dawley (□) rats bred by Japan SLC. Mast cells were incubated at 37°C for 10 min with substance P (upper panel) or neurokinin A (lower panel) at the concentrations indicated. Each point represents the mean ± S.E.M. of four experiments. No error bar represents that the error bar is smaller than the symbol used. Histamine contents of peritoneal mast cells of Std:Wistar, Std:Wistar/ST and Slc:Sprague–Dawley rats were 147.5 ± 7.8, 90.8 ± 12.1 and 160.5 ± 18.5 ng/10^4 mast cells, respectively. Spontaneous histamine release values (% content) from peritoneal mast cells of these rats were 1.5 ± 0.2, 2.1 ± 0.1 and 2.0 ± 0.2%, respectively.

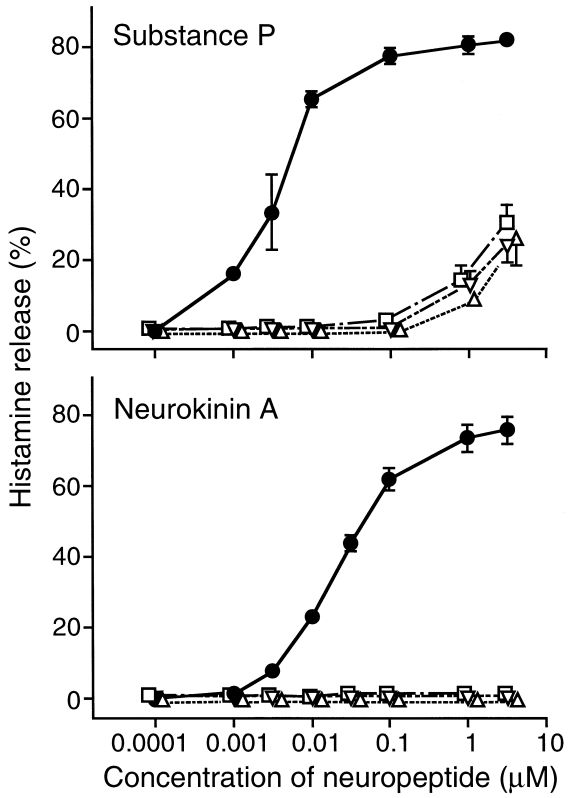

Fig. 2. Substance P- and neurokinin A-induced histamine release from peritoneal mast cells of Wistar rats from several breeders. ●, Std:Wistar; △: Siz:Wistar, □, Sea:Wistar; ▽, Iar:Wistar Imamichi. Mast cells were incubated at 37°C for 10 min with substance P (upper panel) or neurokinin A (lower panel) at the concentrations indicated. Each point represents the mean ± S.E.M. of four experiments. No error bar represents that the error bar is smaller than the symbol used. Histamine contents of peritoneal mast cells of Std:Wistar, Siz:Wistar, Sea:Wistar and Iar:Wistar Imamichi rats were 191.6 ± 13.3, 165.7 ± 20.5, 127.9 ± 21.9 and 151.9 ± 21.5 ng/10^4 mast cells, respectively. Spontaneous histamine release values (% content) from peritoneal mast cells of these rats were 1.2 ± 0.2, 1.1 ± 0.1, 2.4 ± 0.5 and 1.7 ± 0.2%, respectively.

massage, the peritoneal fluid, including mast cells, was collected. The fluid was gently centrifuged ($50 \times g$, 7 min, 4°C, 3 times) to obtain partially purified mast cells. These were further purified according to Sullivan et al. (1975) by centrifugation through a 31.5% bovine serum albumin layer. Mast cells were suspended in Ca^{2+}-free mast cell medium containing 0.1% bovine serum albumin and 0.1% gelatin at a density of 10^4 mast cells/ml. Mast cells were over 95% pure.

2.4. Substance P- or neurokinin A-induced histamine release

Aliquots of the mast cell suspension were distributed into individual tubes (2 ml/tube) and incubated at 37°C for 10 min following the addition of $CaCl_2$ at a final concentration of 0.9 mM. Mast cells were incubated with various or fixed concentrations of substance P, neurokinin A, acetyl-[Arg^6,Sar^9, $Met(O_2)^{11}$]substance P-(6–11) or compound 48/80 for 10 min to assess histamine release. To determine the effects of CP-96345 or SR-48968 on release, various concentrations of the antagonists were added to the suspension 1 min before the agonist. The reaction was stopped by cooling in ice-water followed by centrifugation at $1700 \times g$ for 10 min at 4°C. The supernatant was stored at −20°C until the histamine assay.

2.5. Assay of histamine

Histamine in the supernatant was assayed fluorometrically by high performance liquid chromatography over a cation exchange column (TSK gel SP-2SW, 4.6 Ø × 50 mm, Toso, Tokyo, Japan) as described (Yamamura et al., 1994b). Histamine release is expressed as the percentage of histamine in the supernatant compared with that of cells lysed with 3% perchloric acid. Substance P-, neurokinin A-, acetyl-[Arg^6,Sar^9, $Met(O_2)^{11}$]substance P-(6–11)- and compound 48/80-induced histamine release was calculated by subtracting spontaneous release.

2.6. Statistical analysis

Statistical analyses were performed by the one-way analysis of variance (ANOVA). If significance was detected, individual group differences were evaluated by Bonferroni's multiple test. A probability value (P) below 0.05 was considered statistically significant.

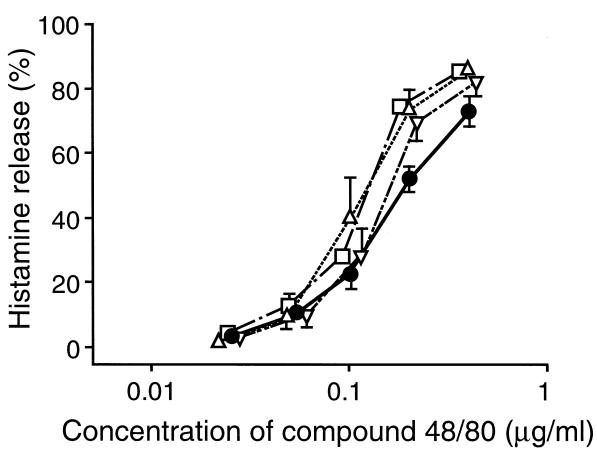

Fig. 3. Compound 48/80-induced histamine release from peritoneal mast cells of Wistar rats from several breeders. ●, Std:Wistar; △, Siz:Wistar; □, Sea:Wistar; ▽, Iar:Wistar Imamichi. Mast cells were incubated at 37°C for 10 min with compound 48/80 at the concentrations indicated. Each point represents the mean ± S.E.M. of three experiments. No error bar represents that the error bar is smaller than the symbol used. Histamine contents of peritoneal mast cells of Std:Wistar, Siz:Wistar, Sea:Wistar and Iar:Wistar Imamichi rats were 187.7 ± 18.7, 172.9 ± 27.1, 133.5 ± 30.0 and 163.3 ± 25.7 ng/10^4 mast cells, respectively. Spontaneous histamine release values (% content) from peritoneal mast cells of these rats were 1.3 ± 0.3, 1.1 ± 0.2, 1.9 ± 0.3 and 1.6 ± 0.2%, respectively.

3. Results

3.1. Ability of peritoneal mast cells of Std:Wistar, Std:Wistar / ST and Slc:Sprague–Dawley rats to release histamine in response to substance P and neurokinin A

Fig. 1 shows whether peritoneal mast cells of Std:Wistar, Std:Wistar/ST and Slc:Sprague–Dawley rats bred by Japan SLC can release histamine in response to substance P and neurokinin A over a wide range of concentrations. Both mast cells of Std:Wistar/ST and Slc:Sprague–Dawley rats released modest amounts of histamine in response to substance P at concentrations of 1 and 3 μM, but not to neurokinin A even at 3 μM. Strikingly different from these, Std:Wistar rat mast cells significantly responded not only to substance P but also to neurokinin A: The cells released histamine concentration-dependently from 0.001 or 0.003–3 μM neuropeptides, reaching approximately

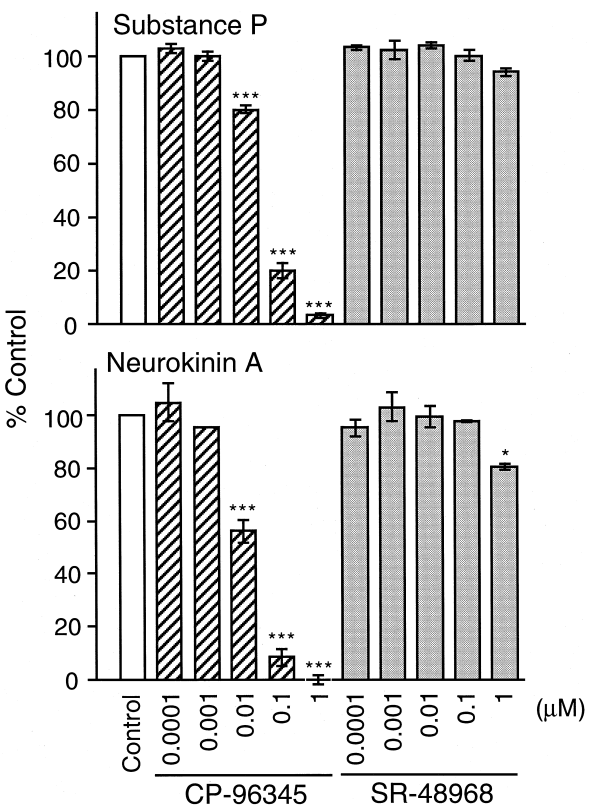

Fig. 4. Effect of CP-96345 and SR-48968 on substance P- and neurokinin A-induced histamine release from peritoneal mast cells of Std:Wistar rats. Mast cells were incubated with CP-96345 or SR-48968 at the concentrations indicated for 1 min followed by substance P (3 nM, upper panel) or neurokinin A (10 nM, lower panel) at 37°C for 10 min. Each column represents the mean ± S.E.M. of three experiments. Histamine content was 196.3 ± 14.3 ng/10^4 mast cells. Spontaneous, and substance P- and neurokinin A-induced histamine release values (% content) were 1.4 ± 0.4, and 41.1 ± 0.8 and 16.7 ± 1.9%, respectively. * and ***: Statistically significant difference from the control at $P < 0.05$ and 0.001, respectively.

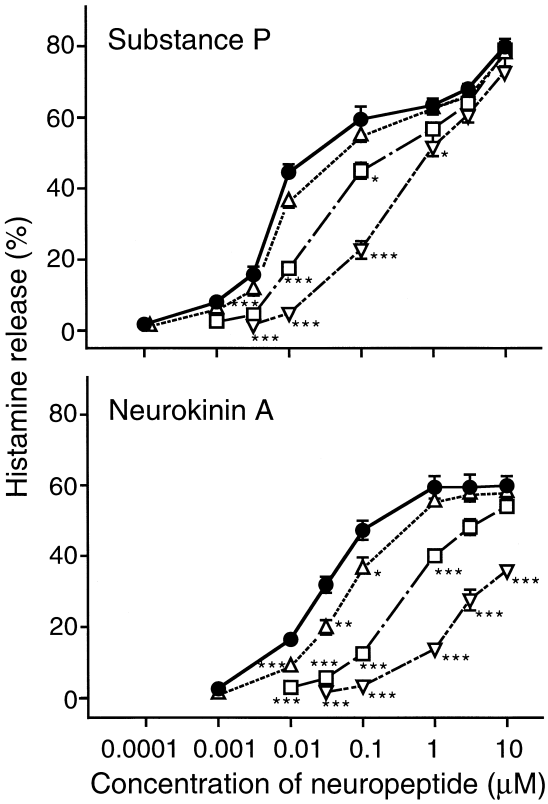

Fig. 5. Concentration–response curves for substance P- and neurokinin A-induced histamine release in the absence (●) or presence of CP-96345 (△, 0.01 μM; □, 0.1 μM; ▽, 1 μM) from peritoneal mast cells of Std:Wistar rats. Mast cells were incubated with CP-96345 for 1 min followed by various concentrations of substance P (upper panel) or neurokinin A (lower panel) at 37°C for 10 min. Each point represents the mean ± S.E.M. of four experiments. No error bar represents that the error bar is smaller than the symbol used. Histamine content was 189.3 ± 9.3 ng/10^4 mast cells. Spontaneous histamine release value (% content) was 1.6 ± 0.2%. *, ** and ***: Statistically significant difference from control at $P < 0.05$, 0.01 and 0.001, respectively.

80% histamine release at 3 μM. Substance P was 3–10 times more potent than neurokinin A on a molar basis.

3.2. Ability of peritoneal mast cells of Wistar rats bred at several sources to release histamine in response to substance P, neurokinin A and compound 48 / 80

Whether or not peritoneal mast cells from Wistar rats purchased from various breeders (Siz:Wistar, Sea:Wistar and Iar:Wistar Imamichi) can release histamine by substance P and neurokinin A was compared with the activity of Std:Wistar rats. The results are presented in Fig. 2. Unlike Std:Wistar rats, mast cells from all other rats had mild or no responses to respective substance P and neurokinin A in terms of histamine release.

On the other hand, Wistar rats from all sources released histamine when the cells were stimulated by compound 48/80. The concentration-histamine release curves were similar, although the responsiveness of Std:Wistar rat mast

cells tended to be lower than those of other rat cells (Fig. 3).

3.3. Effects of CP-96345 and SR-48968 on substance P-, neurokinin A- and compound 48/80-induced histamine release from peritoneal mast cells of Std:Wistar rats

Fig. 4 shows the effects of CP-96345 and SR-48968 on substance P (3 nM)- and neurokinin A (10 nM)-induced histamine releases from peritoneal mast cells of Std:Wistar rats. CP-96345 at a concentration range of 0.01–1 μM concentration-dependently inhibited not only substance P- but also neurokinin A-induced histamine release with significance. At 1 μM, the drug almost completely antagonised these responses. However, both types of stimulated release were not affected by SR-48968 except that neurokinin A-induced release was modestly suppressed by 1 μM SR-48968.

Concentration–response curves of substance P- and neurokinin A-induced histamine release in the absence or presence of 0.01–1 μM CP-96345 are presented in Fig. 5. The concentration–response curve for substance P without the antagonist appeared to be biphasic, consisting of responses to low (to 0.3 μM) and high (3 and 10 μM) concentrations of the agonist. Increasing concentrations of CP-96345 seemed to shift the curve of low substance P concentrations rightward in parallel, but not that for high concentrations of substance P. In contrast, the concentration-histamine release response curve for neurokinin A was parallel-rightward-shifted by CP-96345.

CP-96345 did not inhibit compound 48/80-induced histamine release from the cells (data not shown).

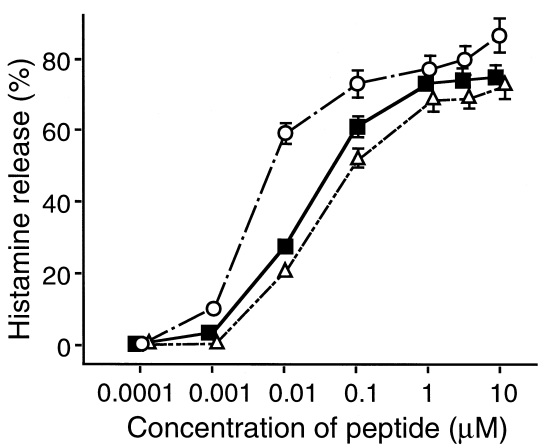

Fig. 6. C-terminal fragment of substance P, acetyl-[Arg^6,Sar^9, Met(O$_2$)^{11}]substance P-(6–11)-, substance P- and neurokinin A-induced histamine release from peritoneal mast cells of Std:Wistar rats. Mast cells were incubated at 37°C for 10 min with acetyl-[Arg^6,Sar^9, Met(O$_2$)^{11}]substance P-(6–11) (■), substance P (○) or neurokinin A (△) at the concentrations indicated. Each point represents the mean ± S.E.M. of three experiments. No error bar represents that the error bar is smaller than the symbol used. Histamine content was 174.3 ± 7.4 ng/10^4 mast cells. Spontaneous histamine release value (% content) was 2.3 ± 0.3%.

3.4. Ability of peritoneal mast cells of Std:Wistar rats to release histamine in response to acetyl-[Arg^6,Sar^9, Met(O$_2$)^{11}]substance P-(6–11)

Whether or not acetyl-[Arg^6,Sar^9, Met(O$_2$)^{11}]substance P-(6–11) induces histamine release from peritoneal mast cells of Std:Wistar rats was evaluated in comparison with the activities of substance P and neurokinin A (Fig. 6). Similar to the effects of substance P and neurokinin A, acetyl-[Arg^6,Sar^9, Met(O$_2$)^{11}]substance P-(6–11) also caused significant histamine release in a concentration-dependent manner. The activity of the substance P fragment was equipotent to that of neurokinin A.

4. Discussion

Substance P but not neurokinin A presumably causes degranulation of rat peritoneal mast cells at micromolar concentrations through direct activation of pertussis toxin-sensitive G proteins bound to the inner face of the plasma membrane, but not through the activation of specific receptors (Mousli et al., 1990). In accordance with that report, peritoneal mast cells of Sprague–Dawley and all Wistar rats tested except Std:Wistar rats responded to substance P but not neurokinin A by releasing histamine at micromolar concentrations. Quite interestingly, peritoneal mast cells from the Wistar substrain, Std:Wistar, potently released histamine in response to substance P at nanomolar concentrations. In addition, this Wistar substrain also released levels of histamine in response to neurokinin A. We cannot conclude that the peritoneal mast cells of Std:Wistar rats release high levels of histamine in response to secretagogues in general, because the degree of compound 48/80-induced histamine release in the present study was similar to that in the cells of Wistar rats inbred by other sources. The histamine release caused by the low concentrations of substance P and neurokinin A was inhibited by the tachykinin NK$_1$ receptor antagonist, CP-96345, but not the tachykinin NK$_2$ receptor antagonist, SR-48968. The ability of substance P and neurokinin A to cause histamine release in the present study was in accord with the affinity of these agonists for the tachykinin NK$_1$ receptor (Regoli et al., 1988). In addition, CP-96345 potently inhibited histamine release induced by substance P at low concentrations and neurokinin A as described above. Therefore, histamine release stimulated by these neuropeptides is mediated by tachykinin NK$_1$ receptors. This is the first report to demonstrate a mechanism of tachykinin NK$_1$ receptor-mediated histamine release from rat peritoneal mast cells.

Similar to the mechanism of compound 48/80-induced histamine release from rat peritoneal mast cells (Nakamura and Ui, 1985; Saito et al., 1987), micromolar concentrations of substance P may directly stimulate G proteins in

the rat peritoneal mast cells to release histamine (Mousli et al., 1989). This activation is caused by the N-terminal domain (arginine and lysine) of the neuropeptide (Mazurek et al., 1981; Fewtrell et al., 1982; Devillier et al., 1985, 1989). In the present concentration–response study of substance P-induced histamine release from peritoneal mast cells of Std:Wistar rats, the response did not reach a plateau even at 30 μM. Furthermore, the release observed at 3 and 10 μM substance P was not inhibited by CP-96345, although histamine release induced by high concentrations of neurokinin A (the N-terminal domain of which lacks arginine but the C-terminal of which is identical with that of substance P) were significantly suppressed by the tachykinin NK_1 receptor antagonist in a concentration-dependent manner. These observations suggest that the mechanisms of histamine release caused by low and high concentrations of substance P are quite different. Low (0.001–1 μM) concentrations of substance P may stimulate tachykinin NK_1 receptor by activity of the C-terminal domain and high (3 and 10 μM) concentrations may directly activate G proteins through the activity of the N-terminal. In addition, the proposed mechanism of histamine release induced by interaction between the C-terminal of substance P and tachykinin NK_1 receptor was indicated by the fact that the C-terminal fragment of substance P, acetyl-[Arg^6,Sar^9, $Met(O_2)^{11}$]substance P-(6–11), also caused histamine release at nanomolar concentrations.

Schild analyses of the concentration–response curves of substance P and neurokinin A in the absence or presence of CP-96345 showed that the inhibitory patterns of the antagonist were both competitive when estimated at 30% histamine release, with pA_2 (slope) of respective 7.65 ± 0.11 (0.99 ± 0.05) and 8.18 ± 0.12 (1.05 ± 0.02). It was reported that pA_2 (slope) of CP-96345 in substance P-induced contraction of isolated guinea-pig main bronchi was 8.06 (0.82), whereas the compound was ineffective against [β-Ala^8]neurokinin A-(4-10), a selective tachykinin NK_2 receptor agonist (Martin et al., 1992). Therefore, the character of the tachykinin NK_1 receptor existing on the peritoneal mast cells appears to be not largely different from that on guinea-pig main bronchial smooth muscle cells. In addition, it is strongly suggested that not only substance P but also neurokinin A stimulates the tachykinin NK_1 receptor on the peritoneal mast cells.

The reason for the different responsiveness to the neuropeptides between Std:Wistar rats and Wistar rats from other sources is unclear. The Wistar strain was established at the Wistar Institute of Biology and Anatomy in the U.S.A. around 1900. Thereafter, the strain spread all over the world and many substrains have been established. Furthermore, genetic variability within Wistar strains has been reported (Yamada et al., 1979). In relation to the expression of tachykinin NK_1 receptors, Mantyh (1991) demonstrated that substance P-binding sites are highly upregulated in surgical samples of the colon from patients with inflammatory bowel disease. In addition, when sensitised mice are challenged by intratracheal administration with antigen, tachykinin NK_1 receptor mRNA levels significantly increase in lymphocytes and macrophages from bronchoalveolar lavage fluid (Kaltreider et al., 1997). Therefore, Std:Wistar rats are useful for investigating diseases mediated by tachykinin NK_1 receptor activation.

On the other hand, Pauwels et al. (1995) reported that Fisher 344 rats have higher airway responsiveness to neurokinin A than BDE rats and that neurokinin A-induced bronchoconstriction in vivo is partly mediated by mast cell activation. Therefore, we also evaluated substance P- and neurokinin A-induced histamine release from peritoneal mast cells of Fisher 344 rats (F344/N Slc, Japan SLC). Both neuropeptides caused histamine release from the cells but to a level that was less than 10% of that observed in Std:Wistar rats (data not shown).

In conclusion, peritoneal mast cells of Std:Wistar rats release high levels of histamine in response to substance P and neurokinin A and this mechanism is completely or partly mediated via tachykinin NK_1 receptor stimulation.

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