



Interactive effect of histamine and prostaglandin D₂ on nasal allergic symptoms in rats

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Abstract

This study was undertaken to investigate the interactive effect of histamine and prostaglandin D₂ in nasal allergic symptoms in rats. The intranasal application of histamine at doses lower than 10 μ mol/site caused no sneezing or nasal rubbing. In addition, prostaglandin D₂ also showed no significant increase in these responses, even at a dose of 10 nmol/site. On the other hand, the simultaneous instillation of histamine and prostaglandin D₂ resulted in a 1000 times more potent effect in inducing nasal symptoms than the administration of histamine alone. Thus, prostaglandin D₂ enhanced the actions of histamine in inducing sneezing and nasal rubbing in a dose-dependent manner, and significant effects were observed at doses higher than 1 nmol/site. The responses induced by the simultaneous application of histamine and prostaglandin D₂ were inhibited by chlorpheniramine, cyproheptadine, BW A868C and ramatroban. Chlorpheniramine and cyproheptadine showed the dose-related inhibition of nasal symptoms induced by the combined administration of histamine (10 nmol) and prostaglandin D₂ (10 nmol), but the effect of cyproheptadine was relatively weak compared with chlorpheniramine. Moreover, BW A868C and ramatroban also showed the inhibition of nasal symptoms induced by the simultaneous administration of histamine and prostaglandin D₂ in a dose-dependent manner. BW A868C was more potent in inhibiting the nasal symptoms than ramatroban. These results clearly indicate that prostaglandin D₂ showed a synergistic effect on sneezing and nasal rubbing induced by histamine in rats, and its effect occurred through both prostaglandin D₂ and CRTH2 (chemoattractant receptor-homologous molecule expressed on TH2 cells) receptors.

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1. Introduction

Prostaglandin D₂ is the major active metabolite of arachidonic acid, and is generated in response to various stimuli to mast cells. It has been reported to contribute in various inflammatory conditions, such as vascular permeability in the nose, skin and conjunctiva, an increase in intranasal pressure, airway narrowing, and eosinophil infiltration in the nose, skin and eye (Naclerio et al., 1983; Charlesworth et al., 1991; Proud et al., 1990; Flower et al., 1976; Woodward et al., 1996; Johnston et al., 1995). In a recent study, Matsuoka et al. (2000)

demonstrated that the repeated administration of antigen exhibited less inflammation in the lung of prostaglandin D₂ (DP) receptor deficient mice than in that of wild-type mice in the asthma model. In addition, prostaglandin D₂ has been shown to induce T helper and eosinophil-dependent inflammation through CRTH2 (chemoattractant receptor-homologous molecule expressed on TH2 cells) receptors (Hirai et al., 2001; Tanaka et al., 2000). Thus, prostaglandin D₂ seems to be an important chemical mediator in various allergic diseases, and its pathological action is currently considered to be elicited through both prostaglandin D₂ receptors (DP₁) and CRTH2 receptors, but its role in nasal allergic signs in animals still remains unclear. However, in an earlier study, we demonstrated through an acute and chronic allergic rhinitis model in rats that histamine and substance P played a significant role in causing the nasal

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allergic signs in rats and selective H₁ antagonists, and tachykinin NK₁ receptor antagonist showed significant inhibition of the nasal symptoms (Ashequr and Kamei, 2005; Rahman et al., 2005). Clinically, however, it has been found that selective H₁ receptor antagonists are unable to alleviate the nasal allergic signs completely, which drove us to investigate the role of other chemical mediators involved in the pathogenesis of nasal allergic symptoms in animals (Howarth and Holgate, 1984; Meltzer et al., 2000). Moreover, it is widely recognized that the basis of allergic rhinitis is the activation of mast cells, eosinophils and basophils, and antigen antibody reactions cause the release of not only histamine, but also other chemical mediators, including leukotrienes, serotonin, prostaglandins, thromboxanes, platelet activating factor, tryptase and kinins. These are also implicated in the pathogenesis of nasal allergic reaction (Burrows et al., 1989; Howarth, 1997; Sugimoto et al., 1994; Naclerio et al., 1991). Recently, Arimura et al. (2001) demonstrated that the prostaglandin D₂ (DP₁) receptor antagonist, S-5751, caused a significant inhibition of sneezing induced by antigen in guinea pigs. Similarly, the thromboxane A₂ receptor antagonist, ramatroban, was also shown to inhibit the sneezing and nasal rubbing induced by antigen in mice and guinea pigs (Kayasuga et al., 2002; Narita et al., 1996). On the other hand, it has been reported that the intranasal application of prostaglandin D₂ and a thromboxane A₂ receptor agonist, U-46619, caused no sneezing in humans and guinea pigs, respectively (Doyle et al., 1990; Yamasaki et al., 2001). Accordingly, Yamasaki et al. (1997) reported that the perfusion of prostaglandin D₂ into the nasal cavity in guinea pigs did not induce the dye exudation more so than the vehicle treatment. In addition, there is some evidence that ramatroban not only acts through thromboxane A₂ (TP) receptors, but also through CRTH2 receptors (Shiraishi et al., 2005). Thus, the mechanisms underlying the inhibition of antigen-induced nasal symptoms with S-5751 and ramatroban have not yet been clearly understood. However, based on the above findings, it is very reasonable to assume that although prostaglandin D₂ and thromboxane A₂ caused no nasal symptoms directly, they may have the capability to enhance the activity of other mediators, which are released from the activated mast cells simultaneously to generate the nasal symptoms. To our knowledge, to date, there are no studies clarifying whether prostaglandin D₂ influence the activity of histamine in inducing allergic nasal symptoms in an animal model. Therefore, in the present study, we investigated the role of prostaglandin D₂ in histamine-induced allergic nasal symptoms in rats using the histamine and prostaglandin D₂ receptor agonist and antagonist.

2. Materials and methods

2.1. Animals

Six week-old male Wistar rats (body weight 180–190 g) were obtained from Japan SLC, Shizuoka, Japan. The animals were housed in an air-conditioned room maintained at 24±2 °C with a relative humidity of 55±15%. They were kept in aluminum cages with sawdust. The rats were given standard laboratory

rodent chow (Oriental Yeast, Tokyo, Japan) and water ad libitum. All procedures involving the animals were conducted in accordance with the Guidelines for Animal Experiments at Okayama University Advanced Science Research Centers, and all procedures were licensed by the Animal Research Control Committee of Okayama University.

2.2. Reagents and drugs

The following reagents and drugs were obtained from the sources shown in parentheses: histamine dihydrochloride (Nacalai Tesque, Kyoto, Japan), prostaglandin D₂ (Cayman Chemical Co., Ann Arbor, MI, USA), chlorpheniramine maleate (Sigma, St. Louis, MO, USA), BW A868C, 3-[(2-cyclohexyl-2-hydroxyethyl) amino]-2,5-dioxo-1-(phenyl-methyl)-4-imidazolidine-heptanoic acid (Cayman Chemical Co., Ann Arbor, MI, USA), cyproheptadine hydrochloride (Sigma, St. Louis, MO, USA), ramatroban (Bayer Yakuin, Osaka, Japan). Histamine is dissolved in saline and 10 µl of histamine solution was administered into the bilateral nasal cavities of the free moving rats. Prostaglandin D₂ was dissolved in saline containing 0.01% ethanol and 10 µl of prostaglandin D₂ solution was administered into the bilateral nasal cavities of the freely moving rats. In the case of simultaneous application, 10 nmol of histamine solution was mixed with 10 nmol of prostaglandin D₂ in a micro tube with a micropipette prior to the intranasal application and 10 µl of the solution was administered into the bilateral nasal cavities. BW A868C was dissolved in saline and administered intravenously 10 min before the histamine and prostaglandin D₂ challenge. Other drugs were suspended in 5% gum arabic solution and administered orally 1 h before the topical application of histamine and prostaglandin D₂. Nasal behavior was measured for 30 min after the instillation of histamine and prostaglandin D₂ into the bilateral nasal cavities with a micropipette.

2.3. Evaluation of nasal behavior

Before the experiment, the animals were placed into a plastic cage (30×18×24 cm) for about 10 min for acclimatization. After the nasal instillation of histamine and prostaglandin D₂ dissolved in physiological saline into the bilateral nasal cavities, the animals were placed into the plastic cage (one animal/cage) and the number of sneezes and nasal rubbing movements were counted for 30 min, in accordance with the method of Ashequr and Kamei (2005). In this study, 10–13 rats were used in each group.

2.4. Effects of test drugs on the nasal behavior

In this study, BW A868C was administered intravenously 10 min before the nasal instillation of histamine (10 nmol/site) and prostaglandin D₂ (10 nmol/site). The other antiallergic drugs were administered orally 1 h before the histamine and prostaglandin D₂ challenge. The numbers of sneezes and nasal rubbing movements induced by histamine and prostaglandin D₂ were counted for 30 min.

2.5. Statistical analysis

Data are presented as means $\pm$ S.E.M. Statistical analysis was performed by one-way analysis of variance with Dunnett's test. A probability value of less than 0.05 was considered significant.

3. Results

3.1. Changes in nasal symptoms induced by histamine and prostaglandin D₂ in rats

Fig. 1 shows the nasal symptoms-induced by the topical application of histamine and prostaglandin D₂ in rats. After the topical application of histamine and prostaglandin D₂ (10 μ l), the nasal symptoms were observed immediately and lasted for 30 min. Histamine caused the increase of sneezing and nasal rubbing movements, and at a dose of 10 μ mol/site it showed significant effects (Fig. 1A). On the other hand, prostaglandin D₂ had no effects in inducing sneezing or nasal rubbing, even at a dose of 10 nmol/site (Fig. 1B).

3.2. Changes in nasal behavior induced by the simultaneous application of histamine and prostaglandin D₂ in rats

The nasal behavior induced by the simultaneous application of histamine and prostaglandin D₂ is shown in Figs. 2 and 3. Fig. 2 showed the dose-dependent increase of sneezing induced by the simultaneous application of histamine and prostaglandin D₂. At doses of 10 nmol/site prostaglandin D₂ and 1 nmol/site histamine, 1 nmol/site prostaglandin D₂ and 10 nmol/site histamine, 10 nmol/site prostaglandin D₂ and 10 nmol/site histamine, respectively, showed significant effects. Fig. 3 also showed the dose-related

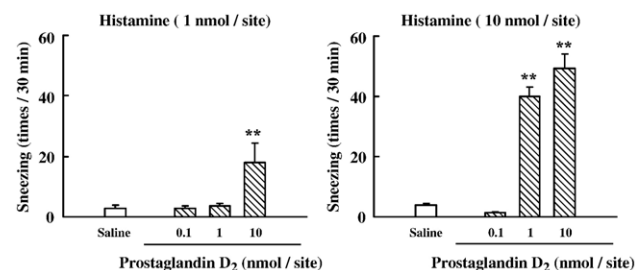


Fig. 2. The number of sneezes induced by the simultaneous application of histamine and prostaglandin D₂ in rats. The number of sneezes was counted immediately after the nasal instillation of histamine and prostaglandin D₂ for 30 min. Each column and vertical bar shows the mean $\pm$ S.E.M. ($n=10-13$). **: Significantly different from the control group at $P<0.01$ (Dunnett's test).

increase of nasal rubbing induced by the simultaneous application of histamine and prostaglandin D₂, and at doses of 10 nmol/site prostaglandin D₂ and 1 nmol/site histamine, 1 nmol/site prostaglandin D₂ and 10 nmol/site histamine, 10 nmol/site prostaglandin D₂ and 10 nmol/site histamine, respectively, showed significant effects.

3.3. Effects of H₁ receptor antagonists, prostaglandin D₂ receptor antagonist and CRTH2 receptor antagonist on sneezing induced by the simultaneous application of histamine (10 nmol/site) and prostaglandin D₂ (10 nmol/site) in rats

Fig. 4 shows the effects of H₁ receptor antagonists, prostaglandin D₂ receptor antagonist and CRTH2 receptor antagonist on the sneezing induced by the simultaneous application of histamine (10 nmol/site) and prostaglandin D₂ (10 nmol/site). Chlorpheniramine and cyproheptadine caused a dose-related inhibition of the number of sneezes induced by the co-administration of histamine and prostaglandin D₂. Significant effects were observed with 3 and 10 mg/kg of chlorpheniramine and 10 mg/kg of cyproheptadine. The selective prostaglandin D₂ receptor antagonist, BW A868C, also caused a decrease in the number of sneezes induced by the histamine and prostaglandin D₂ in a dose-dependent manner, and significant effects were observed with doses of 0.3 and 1 mg/kg. In addition, the CRTH2 receptor antagonist, ramatroban, also

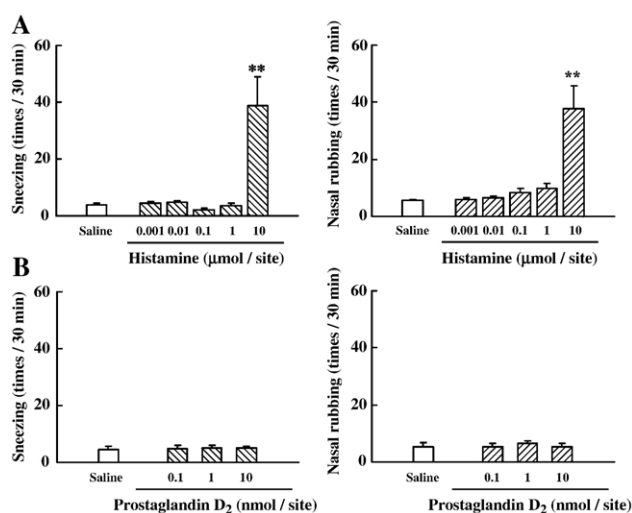


Fig. 1. The numbers of sneezing and nasal rubbing behaviors induced by intranasal application of histamine and prostaglandin D₂ in rats. A: sneezing and nasal rubbing induced by histamine, B: sneezing and nasal rubbing induced by prostaglandin D₂. The nasal symptoms were observed immediately after the nasal instillation of histamine and prostaglandin D₂ for 30 min. Each column and vertical bar shows the mean $\pm$ S.E.M. ($n=10-13$). **: Significantly different from the control group at $P<0.01$ (Dunnett's test).

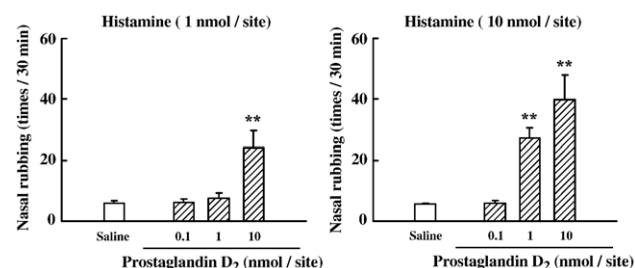


Fig. 3. The number of incidences of nasal rubbing induced by the simultaneous application of histamine and prostaglandin D₂ in rats. The number of incidences of nasal rubbing was counted immediately after the nasal instillation of histamine and prostaglandin D₂ for 30 min. Each column and vertical bar shows the mean $\pm$ S.E.M. ($n=10-13$). **: Significantly different from the control group at $P<0.01$ (Dunnett's test).

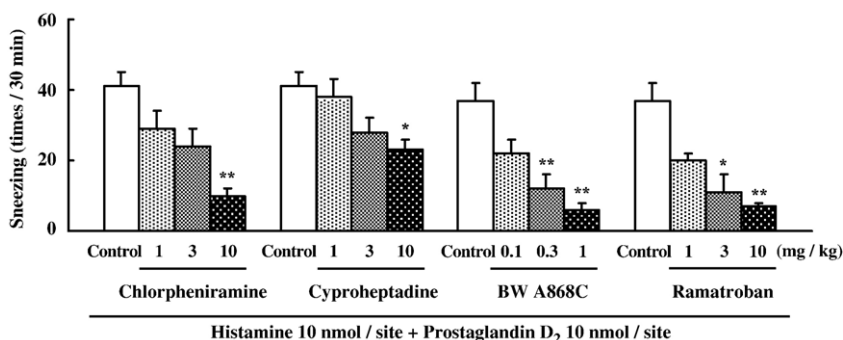


Fig. 4. Effects of H_1 receptor antagonists, prostaglandin D_2 receptor antagonist and CRTH2 receptor antagonist on sneezing induced by the simultaneous application of histamine and prostaglandin D_2 in rats. The prostaglandin D_2 receptor antagonist was administered intravenously 10 min before the topical application of histamine and prostaglandin D_2 . The other drugs were administered orally 1 h before the histamine and prostaglandin D_2 challenge. The nasal behavior was measured immediately for 30 min after the topical application of histamine and prostaglandin D_2 . Each column and vertical bar shows the mean $\pm$ S.E.M. ($n=8-10$). *, **: Significantly different from the control group at $P<0.05$ and $P<0.01$, respectively (Dunnett's test).

showed a reduction of sneezing induced by the histamine and prostaglandin D_2 in a dose-related fashion, and a significant reduction was observed at doses of 3 and 10 mg/kg.

3.4. Effects of H_1 receptor antagonists, prostaglandin D_2 receptor antagonist and CRTH2 receptor antagonists on the nasal rubbing induced by the simultaneous application of histamine (10 nmol/site) and prostaglandin D_2 (10 nmol/site) in rats

Fig. 5 shows the dose-dependent effectiveness of H_1 receptor antagonists, prostaglandin D_2 and CRTH2 receptor antagonists on the nasal rubbing induced by the simultaneous application of histamine (10 nmol/site) and prostaglandin D_2 (10 nmol/site). Chlorpheniramine resulted in dose-related decrease of nasal rubbing induced by the simultaneous application of histamine and prostaglandin D_2 , and significant effects were observed at a dose of 10 mg/kg. Cyproheptadine also caused a dose-related decrease of nasal rubbing induced by the co-administration of histamine and prostaglandin, but significant effects were not observed, even at the dose of 10 mg/kg. Nasal rubbing induced

by the simultaneous application of histamine and prostaglandin D_2 was also inhibited by BW A868C and ramatroban respectively in a dose-dependent manner, and significant effects were observed with BW A868C (0.3 and 1 mg/kg) and ramatroban (3 and 10 mg/kg).

4. Discussion

In this study, we demonstrated that the intranasal application of prostaglandin D_2 caused no nasal symptoms, such as sneezing and nasal rubbing movements in rats, even at a dose of 10 nmol/site. Simultaneously, the present findings also indicated that the topical application of histamine at a dose lower than 1 μ mol/site does not provoke nasal allergic signs in rats. On the other hand, we found that the simultaneous intranasal administration of histamine and prostaglandin D_2 at the concentration where they do not individually induce the nasal symptoms, produced a significant increase of nasal allergic symptoms in rats in a dose-dependent manner. Similar results were also reported in allergic reactions using guinea pigs, indicating that the mixture of prostaglandin D_2 and histamine caused a significant increase in

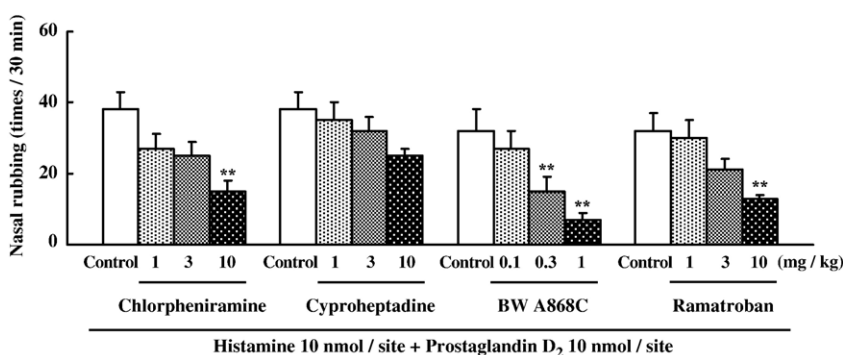


Fig. 5. Effects of H_1 receptor antagonists, prostaglandin D_2 receptor antagonist and CRTH2 receptor antagonist on nasal rubbing induced by the simultaneous application of histamine and prostaglandin D_2 in rats. The prostaglandin D_2 receptor antagonist was administered intravenously 10 min before the topical application of histamine and prostaglandin D_2 . The other drugs were administered orally 1 h before the histamine and prostaglandin D_2 challenge. The nasal behavior was measured immediately for 30 min after the topical application of histamine and prostaglandin D_2 . Each column and vertical bar shows the mean $\pm$ S.E.M. ($n=8-10$). *, **: Significantly different from the control group at $P<0.05$ and $P<0.01$, respectively (Dunnett's test).

the microvascular permeability in the conjunctiva (Arimura et al., 2001). Moreover, prostaglandin D₂ at a dose of 10 ng is known to accelerate the increased vascular permeability in rat skin elicited by 10 µg of histamine (Flower et al., 1976). Therefore, from the above findings, it is very reasonable to consider that although prostaglandin D₂ does not induce nasal symptoms in rats directly, it enhances the ability of histamine to induce these nasal symptoms. It was further found that the nasal symptoms induced by the simultaneous administration of prostaglandin D₂ and histamine was significantly inhibited by the H₁ receptor antagonists chlorpheniramine and cyproheptadine. In association with this, ketotifen was also found to inhibit the plasma exudation induced by the simultaneous application of prostaglandin D₂ and histamine in the conjunctiva in guinea pigs (Arimura et al., 2001). In addition, the present study also revealed that the nasal allergic signs induced by the prostaglandin D₂ and histamine, were also significantly suppressed by the selective prostaglandin D₂ receptor antagonist BW A868C. Plasma exudation induced by antigen in nasal mucosa was also significantly prevented with the pretreatment with BW A868C in guinea pigs (Arimura et al., 2001). Moreover, BW A868C showed a significant inhibition of sneezing induced by antigen and microvascular permeability induced by the simultaneous application of prostaglandin D₂ and histamine, respectively, in guinea pigs, which is consistent with our present study (Arimura et al., 2001). In another study, antigen-induced eosinophil accumulation in the nose was markedly inhibited by BW A868C, and it has been reported that the inhibition of antigen-induced nasal blockage in guinea pigs by BW A868C was mediated not only through the suppression of plasma exudation, but also through the inhibition of increased blood volume in vessels (Atkinson and Kaliner, 1995). In this regards, Nantel et al. (2004) demonstrated that DP receptor mRNA was detected in epithelial goblet cells, serous glands and on the vasculature. From these findings, prostaglandin D₂ in nasal mucosa is assumed to increase in vascular permeability via DP receptor. Therefore, the resultant increase in mucosal permeability would result in an increased amount of histamine reaching c-fiber in nasal mucosa. This might be the mechanism through which simultaneous application of the histamine and prostaglandin D₂ in much lower concentrations elicited the nasal symptoms in rats. Further study using selective inhibitors for prostaglandin D₂ or CRTH2 receptors or prostaglandin D₂ or CRTH2 receptor deficient mice would help to elucidate the clear role of prostaglandin D₂ in histamine-induced nasal allergic disease. We also evaluated the effect of a CRTH2 receptor antagonist, ramatroban, on the nasal symptoms induced by the prostaglandin D₂ and histamine. Ramatroban markedly suppressed the sneezing and nasal rubbing induced by prostaglandin D₂ and histamine in rats. Moreover, evidence has indicated that ramatroban suppressed the nasal symptoms induced by antigens in mice and guinea pigs (Kayasuga et al., 2002; Narita et al., 1996). On the other hand, Yamasaki et al. (2001) demonstrated that the intranasal application of a thromboxane A₂ receptor agonist, U-46619, caused no sneezing in guinea pigs, which prompted us to consider that something other than the thromboxane A₂ receptor may be involved in causing the

nasal symptoms induced by antigen. Indeed, it was demonstrated that the topical application of prostaglandin D₂ results in the significant accumulation of eosinophils in the guinea pigs conjunctiva and the dog trachea (Woodward et al., 1990; Emery et al., 1989). Accordingly, Hirai et al. (2001) noticed that CRTH2, a chemoattractant receptor, leads to TH2 cell, eosinophils, and basophil induction in response to prostaglandin D₂. Furthermore, CRTH2 receptors have been shown to be involved in mast cell-mediated allergic inflammation (Nagata et al., 1999). Therefore, it is very conceivable to suggest that ramatroban showed its effect in inhibiting the nasal symptoms induced by the simultaneous administration of prostaglandin D₂ and histamine by antagonizing the CRTH2 receptors.

In conclusion, the findings of this study suggest an enhancement of histamine-induced nasal allergic signs by prostaglandin D₂ in rats and the drug containing antihistamine and antiprostanoïd effect may be a favorable target for allergic disease therapies.

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