Brief Report

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Cetirizine more potently exerts mast cell-stabilizing property than diphenhydramine

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SUMMARY Cetirizine, a second-generation antihistamine, and diphenhydramine, a first-generation antihistamine, are among the most widely used anti-allergic drugs. In addition to longer duration of action and less incidence of sedative side effects, recent clinical studies also indicate a higher potency of cetirizine than diphenhydramine in the treatment or prevention of allergic disorders. In the present study, using the differential-interference contrast (DIC) microscopy, we examined the effects of cetirizine and diphenhydramine (1 μM to 1 mM) on the degranulation from rat peritoneal mast cells. Using fluorescence imaging of a water-soluble dye, lucifer yellow, we also examined their effects on the deformation of the plasma membrane. At relatively higher concentrations (100 μM, 1 mM), both cetirizine and diphenhydramine significantly reduced the numbers of degranulating mast cells. Of note, at 1 mM, cetirizine more markedly reduced the number than diphenhydramine, almost entirely suppressing the degranulation of mast cells. Additionally, 1 mM cetirizine and levocetirizine, another second-generation antihistamine, almost totally inhibited the process of exocytosis in mast cells and washed out the trapping of the lucifer yellow on the cell surface, while diphenhydramine and chlorpheniramine, another first-generation antihistamine, did not. This study provided *in vitro* evidence for the first time that cetirizine more potently inhibited the process of exocytosis in mast cells than diphenhydramine, indicating its higher potency as a mast cell-stabilizer. Such mast cell-stabilizing property of cetirizine could be ascribed to its counteracting effect on the plasma membrane deformation in degranulating mast cells.

Keywords Cetirizine, diphenhydramine, exocytosis, mast cells, mast cell-stabilizing property

1. Introduction

Antihistamines are widely used in the treatment of allergic disorders, such as seasonal pollinosis, chronic rhinitis, urticaria and allergic conjunctivitis (*1*). Among them, diphenhydramine, a first-generation antihistamine, has commonly been used in clinical practice due to its prompt onset of action and readily availability (*2*). However, studies indicated that cetirizine, a second-generation antihistamine, is more effective and safer than diphenhydramine because of its longer duration of action and less incidence of sedative side effects (*3,4*). Additionally, recent studies in both humans and experimental animals revealed that cetirizine was more potent than diphenhydramine in the treatment or prevention of allergic reactions (*5,6*). Cetirizine and diphenhydramine primarily exert anti-allergic properties by antagonizing histamine H1 receptors in peripheral tissues (*1*). However, the difference in their pharmacological potency strongly suggests the presence of an additional mechanism by which they exert anti-allergic properties. In our previous studies, by continuously monitoring the process of exocytosis in mast cells, we provided *in vitro* evidence that anti-allergic drugs, anti-microbial drugs and corticosteroids exert mast cell-stabilizing properties (*7-11*). In our recent studies, we have additionally revealed that food constituents, such as vitamins, caffeine and catechin, also stabilize mast cells (*12,13*). In the present study, to elucidate the additional mechanism underlying the anti-allergic properties of antihistamines, we directly examined their effects on the degranulation from rat peritoneal mast cells. Here, this study provides *in vitro* evidence for the first time that cetirizine more potently inhibits the process of exocytosis in mast cells than diphenhydramine, showing its higher potency as a mast cell-stabilizer. This study also shows that the mast cell-stabilizing property of cetirizine may be attributable to its counteracting effect on the plasma membrane deformation in degranulating mast cells.

2. Materials and Methods

2.1. Cell sources and preparation

Male Wistar rats no less than 25 weeks old were purchased from The Jackson Laboratory Japan, Inc. (Yokohama, Japan). We profoundly anaesthetized the rats with isoflurane and sacrificed them by cervical dislocation. The protocols for the use of animals were approved by the Animal Care and Use Committee of Miyagi University. As we previously described (*7-14*), we washed rat peritoneum using standard external (bathing) solution which consists of (in mM): NaCl, 145; KCl, 4.0; $CaCl_2$, 1.0; $MgCl_2$, 2.0; HEPES, 5.0; bovine serum albumin, 0.01% (pH 7.2 adjusted with NaOH) and isolated mast cells from the peritoneal cavity. We maintained the isolated mast cells at room temperature (22-24°C) for about 8 hours until use. The suspension of mast cells was spread on a chamber placed on the headstage of an inverted microscope (Nikon, Tokyo, Japan). Mast cells were easily distinguished from other cell types since they included characteristic secretory granules within the cells (*7-14*).

2.2. Quantification of mast cell degranulation

Cetirizine dihydrochloride, purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan), and diphenhydramine hydrochloride, from Wako Pure Chem Ind. (Osaka, Japan), were separately dissolved in the external solution at final concentrations of 1, 10, 100 μM and 1 mM. Levocetirizine dihydrochloride (Tokyo Chemical Industry Co., Ltd.) and chlorpheniramine hydrochloride (Wako Pure Chem Ind.) were dissolved at final concentration of 1 mM. After we incubated mast cells in these solutions or a solution without the drugs, exocytosis was externally induced by compound 48/80 (Sigma-Aldrich Co., St. Louis, MO, USA; final concentration 10 μg/mL) (*7-14*). We obtained bright-field images from randomly chosen 0.1-mm^2 fields of view (10 views from each condition), as described previously (*7-14*). We counted the number of degranulated mast cells (definition; cells surrounded by more than 8 granules outside the cell membrane) and calculated their ratio to all mast cells.

2.3. Lucifer yellow trapping on the cell subsurface

After the mast cells were incubated in the external solutions containing no drug, 1 mM diphenhydramine, chlorpheniramine, cetirizine or levocetirizine for 10 min, exocytosis was externally induced by compound 48/80 (10 μg/mL). Then, the cells were incubated for 5 min at room temperature in the external solution containing a hydrophilic fluorescent dye, lucifer yellow (*7,8,10,14-16*) (Wako, Osaka, Japan; final concentration 10 μM), and washed thoroughly 2 or 3 times with dye-free external solutions. Fluorescent images were taken using a TE 2000-E Nikon Eclipse fluorescence microscope (Nikon, Tokyo, Japan).

2.4. Statistical analyses

Data were analyzed using Microsoft Excel (Microsoft Corporation, Redmond, Wash., USA) and reported as means ± SEM. Statistical significance was assessed by two-way ANOVA. A value of $p < 0.05$ was considered significant.

3. Results and Discussion

Mast cells incubated in the external solution alone or relatively lower concentrations of diphenhydramine (1, 10 μM) showed a lot of wrinkles on the cell surface and released secretory granules as a consequence of exocytosis (Figures 1Ab-d *vs*. 1Aa). However, in mast cells incubated in relatively higher concentrations of diphenhydramine (100 μM, 1 mM), these findings of exocytosis were partially or almost totally absent (Figures 1Ae and 1Af). Quantitatively, relatively lower concentrations of diphenhydramine (1, 10 μM) did not affect the numbers of degranulating mast cells (Figure 1B). In contrast, 100 μM diphenhydramine significantly decreased the number of degranulating mast cells (external solution, 84.0 ± 3.26% *vs.* 100 μM diphenhydramine, 73.8 ± 3.47%; $n = 13$, $p < 0.05$), and 1 mM diphenhydramine further reduced the number of degranulating cells (41.2 ± 8.50 %; $n = 13$, $p < 0.05$; Figure 1B).

Like the effects of diphenhydramine (Figure 1), relatively lower concentrations of cetirizine (1, 10 μM) did not affect the degranulation of mast cells (Figures 2Ac, 2Ad *vs.* 2Ab) and the numbers of degranulating cells were almost comparable to those incubated in the external solution alone (Figure 2B). However, relatively higher concentrations of cetirizine (100 μM, 1 mM) partially or entirely halted the process of exocytosis (Figures 2Ae and 2Af). Quantitatively, similarly to the effects of diphenhydramine (Figure 1B), 100 μM cetirizine significantly reduced the number of degranulating mast cells (external solution, 92.0 ± 0.99% *vs.* 100 μM cetirizine, 76.2 ± 4.42%; $n = 10$, $p < 0.05$; Figure 2B). However, differing from the effects of diphenhydramine (Figure 1B), 1 mM cetirizine showed more marked reduction, almost totally suppressing the number of degranulating mast cells (2.64 ± 1.03 %; $n = 10$, $p < 0.05$; Figure 2B).

In addition to the exocytotic release of chemical mediators, including histamine, leukotrienes and serotonin, mast cells produce various kinds of proinflammatory cytokines or growth factors (*17*). Therefore, to accurately determine the ability of drugs or substances on the stabilization of mast cells, the exocytotic process itself needs to be directly monitored,

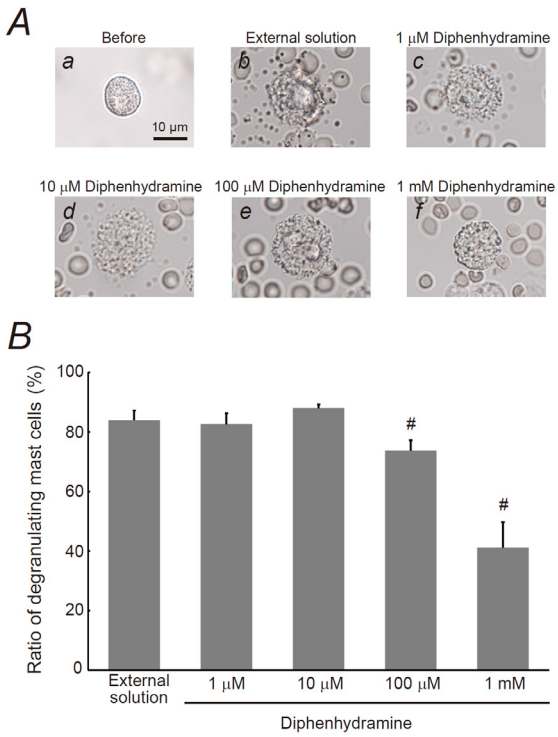

Figure 1. Effects of diphenhydramine on mast cell degranulation. **A**: Differential-interference contrast (DIC) microscopic images were taken before (*a*) and after exocytosis was externally induced by compound 48/80 in mast cells incubated in the external solutions containing no diphenhydramine (*b*), 1 μM diphenhydramine (*c*), 10 μM diphenhydramine (*d*), 100 μM diphenhydramine (*e*) and 1 mM diphenhydramine (*f*). **B**: After the mast cells were incubated in the external solutions containing no diphenhydramine or different concentrations (1, 10, 100 μM and 1 mM) of diphenhydramine, exocytosis was induced by compound 48/80. The numbers of degranulating mast cells were expressed as percentages of the total mast cell numbers in selected bright fields. $^{\#}p < 0.05$ *vs.* incubation in the external solution alone. Values are means ± SEM. Differences were analyzed by ANOVA followed by Dunnett's *t* test.

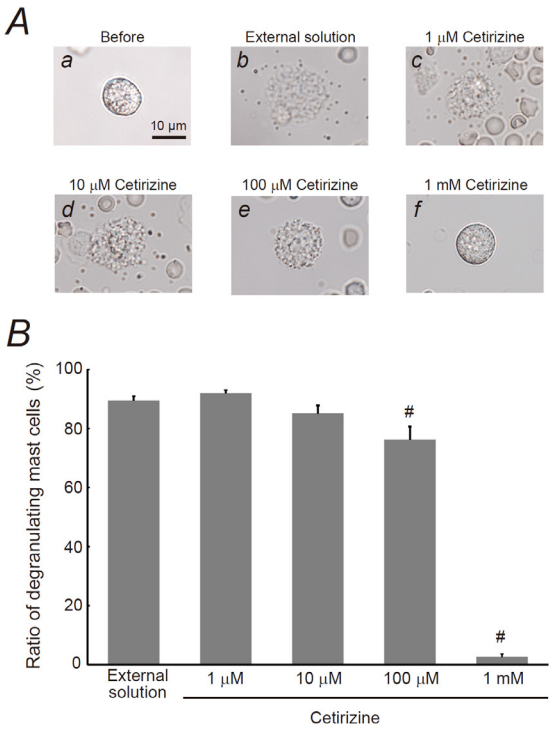

Figure 2. Effects of cetirizine on mast cell degranulation. **A**: Differential-interference contrast (DIC) microscopic images were taken before (*a*) and after exocytosis was externally induced by compound 48/80 in mast cells incubated in the external solutions containing no cetirizine (*b*), 1 μM cetirizine (*c*), 10 μM cetirizine (*d*), 100 μM cetirizine (*e*) and 1 mM cetirizine (*f*). **B**: After the mast cells were incubated in the external solutions containing no cetirizine or different concentrations (1, 10, 100 μM and 1 mM) of cetirizine, exocytosis was induced by compound 48/80. The numbers of degranulating mast cells were expressed as percentages of the total mast cell numbers in selected bright fields. $^{\#}p < 0.05$ *vs.* incubation in the external solution alone. Values are means ± SEM. Differences were analyzed by ANOVA followed by Dunnett's *t* test.

instead of just quantifying the amount of histamine alone (*7,8,10*). In our series of *in vitro* studies using rat peritoneal mast cells, we carefully observed the whole process of exocytosis under the microscope and actually counted the numbers of degranulating mast cells (*7-11*). Thus, we have provided *in vitro* evidence so far that anti-allergic drugs (tranilast, olopatadine, ketotifen, loratadine), anti-microbial drugs (clarithromycin), corticosteroids (hydrocortisone, dexamethasone) and catecholamines (adrenaline) exert mast cell-stabilizing properties (*7-11*). Additionally, we have revealed in our recent studies that food constituents, such as vitamins (ascorbic acid, pyridoxine), caffeine and catechin, also stabilize mast cells, and that such effects were synergistically enhanced by the combination of these constituents (*12,13*). In the preset study, using the same approach, we provided direct evidence for the first time that cetirizine and diphenhydramine dose-dependently inhibited the process of exocytosis. In addition to their primary pharmacological property of blocking histamine receptors, these antihistamines also exerted mast cell-stabilizing properties at high concentrations (Figure 4).

In humans, the serum concentrations of cetirizine and diphenhydramine reaches around 0.5 and 1 μM when physiological doses were orally administered (*18,19*). However, according to *in vitro* studies using microorganisms or cultured human epithelial cells, concentrations as high as 500 μM to 1 mM cetirizine and diphenhydramine were required to additionally elicit their antibacterial properties (*20,21*). Therefore, in the present study, we tried doses starting from 1 μM up to 1 mM. Mast cells that are derived from mucosal tissues, including conjunctiva, are known to produce larger amounts of chemical mediators than those from serosal tissues, including the peritoneal cavity (*22*). Therefore, in previous studies, mast cells derived from human conjunctiva actually required extremely high doses of antihistamines to effectively elicit their anti-allergic properties (*23*). In this regard, the present findings indicated the potency of cetirizine and diphenhydramine in the topical use for allergic conjunctivitis or urticaria.

From our results, at 1 mM, cetirizine more markedly

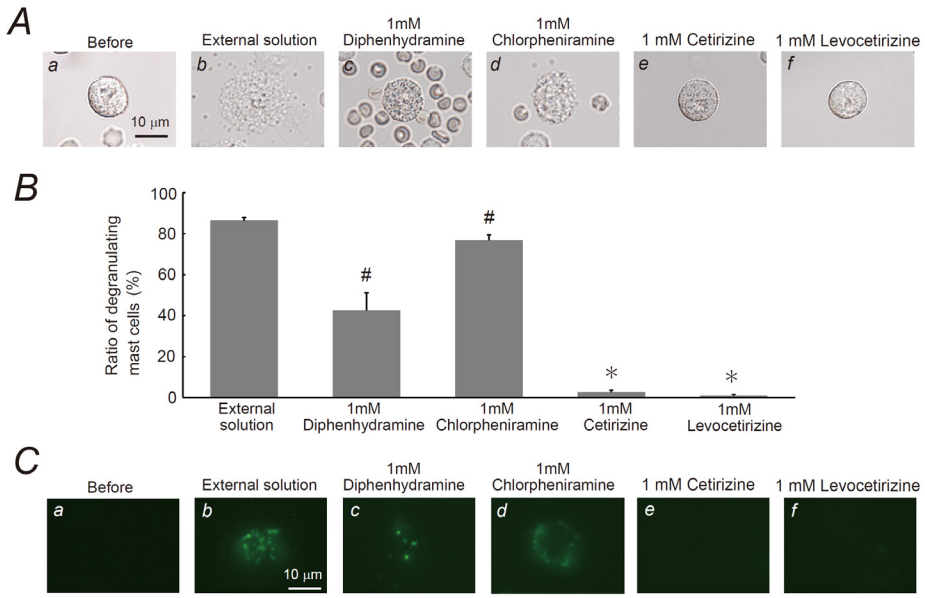

Figure 3. Effects of high concentrations of antihistamines on mast cell degranulation. A: Differential-interference contrast (DIC) microscopic images were taken before (*a*) and after exocytosis was externally induced by compound 48/80 in mast cells incubated in the external solutions containing no antihistamines (*b*), 1 mM diphenhydramine (*c*), 1 mM chlorpheniramine (*d*), 1 mM cetirizine (*e*) and 1 mM levocetirizine (*f*). **B**: After the mast cells were incubated in the external solutions containing no antihistamines or 1 mM antihistamines (diphenhydramine, chlorpheniramine, cetirizine or levocetirizine), exocytosis was induced by compound 48/80. The numbers of degranulating mast cells were expressed as percentages of the total mast cell numbers in selected bright fields. $^{\#}p < 0.05$ *vs.* incubation in the external solution alone. $^{*}p < 0.05$ *vs.* incubation in the external solution containing 1 mM diphenhydramine. Values are means ± SEM. Differences were analyzed by ANOVA followed by Dunnett's *t* test.

reduced the number of degranulating mast cells than diphenhydramine did (Figure 2B *vs.* 1B). To clarify the difference in the mast cell-stabilizing properties between first- and second-generation antihistamines, we also examined the effects of chlorpheniramine and levocetirizine, another first- and second-generation antihistamines, at 1 mM (Figure 3). Using the same approach in our established experimental settings, we've previously confirmed that several mast cell stabilizers, such as tranilast, adrenaline and olopatadine, markedly reduced the number of degranulating mast cells and thus inhibited the process of exocytosis (*7,8,11*). Therefore, these findings were regarded as the positive control for the following experiment. Similarly to the effects of diphenhydramine, 1 mM chlorpheniramine partially halted the process of exocytosis in mast cells (Figure 3Ac, 3Ad *vs.* 3Ab) and significantly reduced the numbers of degranulating cells (external solution, 86.5 ± 1.43% *vs.* 1 mM diphenhydramine, 42.4 ± 8.74%, $n = 13$, $p < 0.05$; 1 mM chlorpheniramine, 76.7 ± 2.68%, $n = 12$, $p < 0.05$; Figure 3B). In contrast, in mast cells incubated in 1 mM cetirizine or levocetirizine, the findings suggestive of exocytosis were almost completely absent (Figure 3Ae, 3Af) and the numbers of degranulating mast cells were almost entirely lost (1 mM cetirizine, 2.55 ± 0.99%, $n = 10$; 1 mM levocetirizine, 0.86 ± 0.61%, $n = 11$; Figure 3B). These findings strongly suggested that the second-generation antihistamines, such as cetirizine and levocetirizine, are highly potent as mast cell-stabilizers

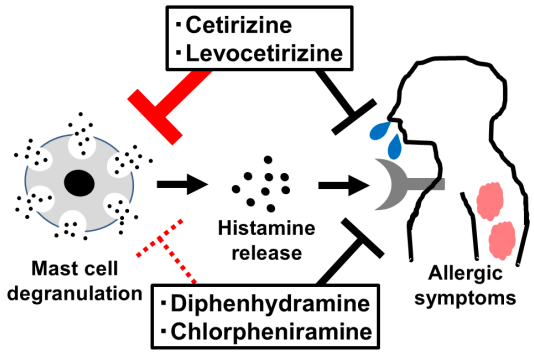

Figure 4. Mast cell-stabilizing properties of antihistamines. Allergic reaction consists of degranulation from mast cells (exocytosis), release of histamine and stimulation of tissue histamine H1 receptors. This causes allergic symptoms, such as sneezing, runny nose (allergic rhinitis), rash and itching (urticaria). In addition to their primary pharmacological property of blocking histamine receptors, antihistamines also exerted mast cell-stabilizing properties at high concentrations. Of note, the second-generation antihistamines, such as cetirizine and levocetirizine, are much more potent than the first-generation antihistamines, such as diphenhydramine and chlorpheniramine, in stabilizing mast cells.

(Figure 4), and that they are much more potent than the first-generation antihistamines, such as diphenhydramine and chlorpheniramine (Figure 4).

In recent studies in humans or experimental animals, cetirizine was more effective than diphenhydramine in the treatment or prevention of allergic reactions (*4-6*).

This may be attributable to the difference in the mast cell-stabilizing properties between these antihistamines as we demonstrated in the present study (Figures 3A and 3B). In addition to allergic reactions, mast cells were also responsible for the development and progression of organ fibrosis, such as liver cirrhosis, renal fibrosis and lung fibrosis (*24-26*). These studies indicated the pharmacological efficacy of suppressing the mast cell activity in the treatment or protection against organ fibrosis. In our previous study, tranilast, a potent mast cell-stabilizer, actually improved peritoneal fibrosis in rats under uremic condition (*27*). Given the highly potent mast cell-stabilizing property of cetirizine (Figure 4), the administration of this drug may also be beneficial in the treatment of organ fibrosis in addition to allergic diseases.

In our previous studies, drugs such as chlorpromazine, salicylate, olopatadine, ketotifen and clarithromycin, changed the plasma membrane curvature in rat peritoneal mast cells (*7,8,10,14*), and thereby regulated the process of exocytosis. In the present study, since 1 mM cetirizine and levocetirizine almost completely inhibited the exocytosis of mast cells (Figures 3A and 3B), the drug-induced alteration of the membrane architecture may also affect the exocytosis. To determine whether the wrinkles observed in the degranulating mast cells (Figure 3A) represented the membrane surface deformation caused by exocytosis, we finally used lucifer yellow (Figure 3C), a water-soluble fluorescent dye which is retained in the invaginated folds generated in the plasma membranes (*7,10,15,16*). In mast cells that were treated with external solution alone, 1 mM diphenhydramine or 1 mM chlorpheniramine, lucifer yellow was trapped almost entirely or at least partially on the cell surface area (Figures 3Cb-3Cd). Because the dye, which is usually membrane-impermeable (*28*), was almost totally absent in the cells before exocytosis was induced (Figure 3Ca), the staining indicated its retention in the opened pores created by exocytosis (*7,8,10,14,29*). However, after incubating mast cells in 1mM cetirizine or 1 mM levocetirizine (Figures 3Ce and 3Cf), the dye was almost completely washed out. These results indicated that cetirizine or levocetirizine inhibited the creation of the invaginated folds when they exerted mast cell-stabilizing properties. This suggested that these antihistamines counteracted the membrane surface deformation caused by exocytosis.

Cetirizine and levocetirizine are zwitterionic at physiological pH and less lipophilic compared to their cations (*30*). Therefore, they are less likely to be accumulated inside the plasma membranes (*31*). Instead, they can directly interact with the polar headgroups of phospholipids (*31*), and thus actually induced changes in the plasma membrane fluidity and its heterogeneity (*32*). In secretory cells, such as lung alveolar cells and mammary gland cells, the process of exocytosis can be modulated by mechanical stimuli to the membranes, including changes in the membrane tension, shear stress, hydrostatic pressure and compression (*8,10,33*). Therefore, such counteracting effects of cetirizine or levocetirizine on the plasma membrane deformation in degranulating mast cells were likely to be responsible for their mast cell-stabilizing properties.

In summary, this study provided *in vitro* evidence for the first time that cetirizine more potently inhibited the process of exocytosis in mast cells than diphenhydramine, indicating its higher potency as a mast cell-stabilizer. Such mast cell-stabilizing property of cetirizine could be ascribed to its counteracting effect on the plasma membrane deformation in degranulating mast cells.

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RF and AA performed the experiments and analyzed the data. MA helped analyze the data. IK designed the experiments, interpreted the results and wrote the paper. All authors read and approved the final manuscript. This study was performed in accordance with the guide for the care and use of laboratory animals of Miyagi University, which included ethical considerations.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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