ELSEVIER

European Journal of Pharmacology 362 (1998) 53–59

ejp

Role of histamine H_1 and H_2 receptor antagonists in the prevention of intimal thickening

Norio Miyazawa [a], Shinji Watanabe [b], Akihisa Matsuda [a], Kazunao Kondo [a], Hisakuni Hashimoto [b], Kazuo Umemura [a,*], Mitsuyoshi Nakashima [a]

[a] *Department of Pharmacology, Hamamatsu University School of Medicine, 3600, Handa-cho, Hamamatsu 431-3192, Japan*
[b] *Department of Pharmacology, Hospital Pharmacy, Hamamatsu University School of Medicine, 3600, Handa-cho, Hamamatsu 431-3192, Japan*

Received 4 August 1998; revised 25 September 1998; accepted 2 October 1998

Abstract

Vascular smooth muscle cell migration to the intima from the media and proliferation in the intima play key roles in atherosclerosis and restenosis after coronary angioplasty. Histamine released from adherent platelets at the injured artery and from mast cells in atheromas has stimulant actions on both smooth muscle cell migration and proliferation, and histamine receptor antagonists abolish the effect of histamine in vitro. The aim of this study was to examine the effect of histamine receptor antagonists on intimal thickening. Endothelial injury in the mouse femoral artery was induced by a photochemical reaction between localized irradiation by green light and intravenously administered rose bengal. The histamine H_1 receptor antagonist, diphenhydramine, at a dose of 30 mg/kg or the histamine H_2 receptor antagonist, cimetidine, at a dose of 200 mg/kg was intraperitoneally administered to mice for 21 days after endothelial injury. Twenty-one days after endothelial injury, morphometric analysis was performed to measure the cross-sectional areas of the intima and media. Diphenhydramine significantly reduced the intimal area to 1.1 ± 0.3 ($\times 10^{-3}$ mm^2) compared with the value in the control group, which was 6.2 ± 1.4 ($\times 10^{-3}$ mm^2), but cimetidine (5.5 ± 1.9, $\times 10^{-3}$ mm^2) did not. Similarly, the ratio of intimal area to medial area in the diphenhydramine-treated group but not in the cimetidine-treated group was significantly reduced (83%). In the in vitro study, cimetidine inhibited neither proliferation nor migration of mouse vascular smooth muscle cells stimulated by platelet-derived growth factor (PDGF). In contrast, diphenhydramine significantly ($P < 0.05$) inhibited proliferation in a dose-dependent manner, but did not inhibit migration. These results suggest that diphenhydramine, a histamine H_1 receptor antagonist, reduced the formation of intimal hyperplasia, at least in part due to inhibition of cell proliferation. However, cimetidine, a histamine H_2 receptor antagonist, was ineffective. Histamine may play a key role in intimal thickening, in part via histamine H_1 receptors in this model.

Keywords: Diphenhydramine; Cimetidine; Intimal thickening; Endothelial injury; Migration; Proliferation

1. Introduction

Percutaneous transluminal coronary angioplasty has become a well-established technique for myocardial revascularization of patients with ischemic heart disease, such as unstable angina or evolving myocardial infarction. However, percutaneous transluminal coronary angioplasty remains limited by the restenosis that occurs in approximately 30–40% of cases despite a successful procedure (Kaltenbach et al., 1985; Bauters et al., 1996). The endothelium is inevitably removed and the subendothelium of an artery is exposed after percutaneous transluminal coronary angioplasty, which results in platelet adhesion and aggregation on the subendothelium at the site of the inflated artery. Activated platelets have been shown to release platelet-derived growth factor (PDGF), transforming growth factor β, noradrenaline, adenosine 5′-diphosphate, serotonin and histamine from α-granules (Bottaro et al., 1985; Bell and Madri, 1989; Crowley et al., 1994). These platelet products are thought to stimulate the migration of vascular smooth muscle cells to the intima from the media and their proliferation in the intima. These events play a key role in the formation of intimal hyperplasia (Ross, 1986, 1993; Liu et al., 1989). However, although much attention has been focused on the contribution of peptide growth factors, especially PDGF, to the formation of intimal thickening, little is known about the role of non-peptide platelet products, such as histamine, in this process. Recently, the presence of mast cells, which are

* Corresponding author. Tel.: +81-53-435-2269; Fax: +81-53-435-2269; E-mail: umemura@hama-med.ac.jp

0014-2999/98/$ - see front matter
PII: S0014-2999(98)00716-X

known as the storage sites of histamine, in human coronary atheromas was demonstrated by immunohistochemistry (Kaartinen et al., 1996a,b), and we and other investigators (Mannaioni et al., 1997; Metzler and Xu, 1997) suspect that histamine released from mast cells as well as platelets contributes to the formation of intimal thickening. Furthermore, mast cell stabilizers, tranilast and pemirolast, prevent intimal hyperplasia not only in rats (Kikuchi et al., 1996; Miyazawa et al., 1997) but also in humans (The TREAT study investigators, 1994; Ohsawa et al., 1995).

Histamine stimulates both the migration (Bottaro et al., 1985; Bell and Madri, 1989) and the proliferation (Bell and Madri, 1989) of vascular smooth muscle cells and amplifies the proliferation stimulated by PDGF (Crowley et al., 1994). Furthermore, histamine induces the expression of the adhesion molecule P-selectin on the endothelium and induces subsequent leukocyte rolling (Asako et al., 1994; Eppihimer et al., 1996), which is a key step in the transmigration of monocytes/lymphocytes into the subendothelium. Infiltrated lymphocytes that differentiate into macrophages release growth factors, such as PDGF (Morisaki et al., 1992), transforming growth factor β (Bahadori et al., 1995), and basic-fibroblast growth factor (Greisler et al., 1993). A histamine H_1 receptor antagonist, diphenhydramine, inhibits the amplification of the proliferation stimulated by PDGF (Crowley et al., 1994) and inhibits the histamine-induced P-selectin upregulation on the endothelial cell surface (Asako et al., 1994; Eppihimer et al., 1996). A histamine H_2 receptor antagonist, cimetidine, inhibits the migration of smooth muscle cells stimulated by histamine (Bell and Madri, 1989) and inhibits the proliferation of human colon cancer cells (Adams et al., 1994). These effects of histamine receptor antagonists are thought to be due to an inhibition of the formation of intimal hyperplasia. Therefore, we investigated the effect of histamine receptor antagonists, a histamine H_1 receptor antagonist, diphenhydramine, and a histamine H_2 receptor antagonist, cimetidine, on intimal thickening after endothelial injury in the mouse.

2. Materials and methods

2.1. Materials

Diphenhydramine and cimetidine were purchased from Wako (Osaka, Japan) and Fujisawa Pharmaceutical (Osaka, Japan), respectively. These drugs were used after being dissolved in and diluted with saline. Recombinant human PDGF-BB was obtained from Funakoshi (Tokyo, Japan). Fetal bovine serum was from GIBCO BRL (Life Technologies, Rockville, MD, USA).

2.2. Endothelial injury by photochemical reaction

ICR male mice weighing approximately 20 g were purchased from SLC (Hamamatsu, Japan) and kept in cages on a 12-h day/night cycle and fed a regular chow. Thirty animals were divided into 3 groups, which included a control group ($n = 12$), and were administered diphenhydramine ($n = 7$) or cimetidine ($n = 8$) intraperitoneally once a day at dosages of 30 and 200 mg/kg, respectively. Drug administration began the day after endothelial injury was induced and was continued until the animals were killed. Intimal thickening in the femoral artery of mice was produced by photochemically induced endothelial injury as described previously (Miyazawa et al., 1997; Kikuchi et al., 1998). Briefly, animals were anesthetized by intraperitoneal injection of pentobarbital at a dosage of 80 mg/kg and a cannula was inserted into the jugular vein for rose bengal administration. The left femoral artery was carefully exposed, and a laser flow probe (ALF 2100, Advance, Tokyo, Japan) was attached to monitor blood flow. Trans-illumination with green light (wavelength of 540 nm) was achieved using a xenon light with both a heat-absorbing filter and a green filter (L4887, Hamamatsu Photonics, Hamamatsu, Japan). Irradiation was directed via an optic fiber positioned 5 mm away from a segment of intact femoral artery proximal to the flow probe. Irradiation, at a dose of 0.8 W/cm^2, was started when the baseline blood flow was stable. Rose bengal (20 mg/kg) was then injected for 5 min and irradiation was continued for another 10 min. Doses of irradiation and rose bengal were fixed to give a ratio of intimal area to medial area of about 0.6 in control animals. Thirty minutes after rose bengal administration, the wound was closed. The animals were maintained as described above until they were killed after recovery from anesthesia. The protocol in this study was approved by the local ethics committee.

2.3. Histological analysis

The femoral artery was removed from each mouse for histopathological examination 21 days after endothelial injury. Vessels were perfusion-fixed in situ with 1% paraformaldehyde and 2% glutaraldehyde in 0.1 M phosphate-buffered saline at pH 7.4. Then, the femoral artery was removed and fixed further by overnight immersion in the same fixative. The specimens were sectioned transversely and stained with hematoxylin and eosin for light microscopy. The cross-sectional areas of the intima and media were calculated using a computerized apparatus (Video Micro Meter Model VM-30, Olympus, Tokyo, Japan).

2.4. Cell culture

Aortic vascular smooth muscle cells were isolated from the thoracic aortas of ICR male mice (8 weeks) by enzymatic dissociation, using the method of Kobayashi et al. (1993) with some modifications. Briefly, the aorta was incubated with 1.3 mg/ml type 1 collagenase and

0.3 U/ml type 1 elastase (Sigma, St. Louis, MO) in Hanks' solution for 40 min at 37°C, the adventitia was gently removed, and then the aorta was incubated further with 2 mg/ml type 1 collagenase and 3.0 U/ml type 1 elastase in Hanks' solution for 1 h at 37°C. Isolated vascular smooth muscle cells were grown at 37°C in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum, penicillin (100 U/ml), streptomycin (50 mg/ml) and kanamycin (100 mg/ml) in a humidified atmosphere of 5% CO_2 in air. Vascular smooth muscle cells were used up to the 15th passage.

2.5. Cell migration

The migration of mouse vascular smooth muscle cells was assayed by the modified Boyden chamber method, using a microchemotaxis chamber and a polycarbonate membrane filter with pores of 8 μm diameter (Nucleopore, Pleasanton, CA). The drugs were placed in the upper and lower chambers, and 10 ng/ml PDGF-BB was placed in the lower chamber. Mouse vascular smooth muscle cells were detached from the culture dish by trypsin treatment, centrifuged and resuspended at 105 cells/ml in fetal bovine serum-starved medium containing 0.1% bovine serum albumin. Then, the cell suspensions were loaded into the upper chamber and incubated for 4 h at 37°C in a humidified atmosphere containing 5% CO_2 in air. The filter was fixed and stained with diff-quik (Green Cross, Osaka, Japan). The number of vascular smooth muscle cells that migrated to the lower surface of the filter was determined in 4 fields (0.25 mm^2) by using a light microscope.

2.6. Cell proliferation

Vascular smooth muscle cells (2×10^4/well) were applied to 24-well plates in growth medium (DMEM plus 10% fetal bovine serum). After the vascular smooth muscle cells had grown to 70–80% confluence, they were rendered quiescent by incubation for 48 h in DMEM containing 0.1% bovine serum albumin. Medium was replaced by serum-free medium, and the cells were stimulated immediately with recombinant human PDGF-BB (R&D Systems, Minneapolis, MN). During the last 6 h of the 24-h incubation with growth factor, vascular smooth muscle cells were labeled with [methyl-^{3}H]thymidine (Amersham, Braunschweig, Germany) at 18.5 kBq/ml. After incubation, the incorporation of [^{3}H]thymidine into DNA was stopped by removal of the labeled medium. Then, the cells were washed three times with ice-cold PBS (−) and fixed for 15 min with ice-cold 10% trichloroacetic acid. Acid-insoluble [^{3}H]thymidine was extracted into 0.2 ml of 0.4 N NaOH, and this solution was mixed with 5 ml scintillant (Hionic fluor; Packard, Meriden, CT) and counted in a liquid scintillation counter (LS 5000TS; Beckman, Fullerton, CA).

2.7. Statistical analysis

Data represent the mean ± S.E.M. values. Statistical analysis was performed by using a Bonferroni/Dunn type multiple comparison test followed by analysis of variance (ANOVA). Differences were considered to be significant at $P < 0.05$.

3. Results

3.1. Effects of histamine receptor antagonists on intimal thickening

Twenty-one days after endothelial injury, intimal thickening was observed in the subendothelial layers of the drug-untreated animals, an example of which is shown Fig. 1a. Intimal thickening in animals receiving diphenhy-

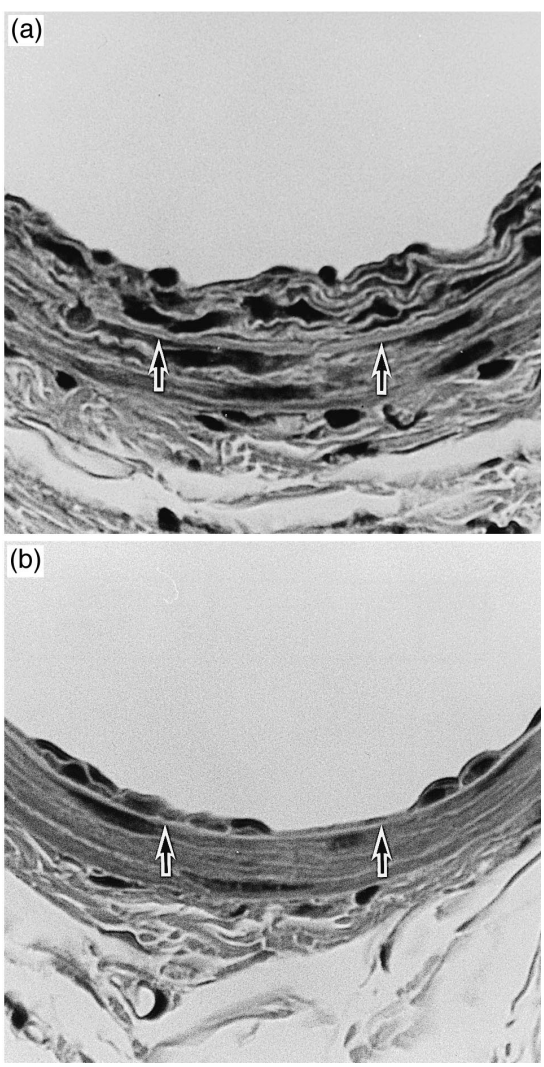

Fig. 1. Light micrographs of representative histological cross-sections from mouse femoral artery segments 21 days after photochemically induced endothelial injury. (a) Injured vessel (b) Injured vessels treated with diphenhydramine. The internal elastic lamina is indicated by arrows in (a) and (b). Hematoxylin-eosin stain (original magnification ×200).

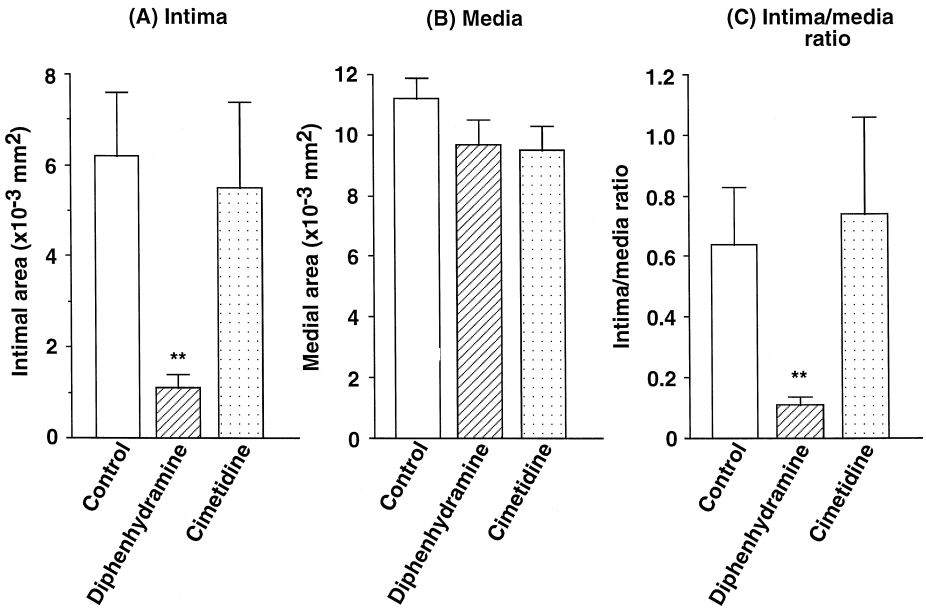

Fig. 2. Effects of diphenhydramine and cimetidine on (A) intimal area, (B) medial area and (C) intima/media ratio of mouse femoral artery 21 days after photochemically induced endothelial injury in control ($n = 12$), and animals treated with diphenhydramine ($n = 7$) and cimetidine ($n = 8$). Data represent means ± S.E.M. values. $**$ $P < 0.01$ vs. control.

dramine was distinctly decreased (Fig. 1b) compared with that in the control animals. However, intimal thickening in animals receiving cimetidine did not differ from that of control animals. The values obtained for the cross-sectional areas of the intima in the injured femoral arteries are shown in Fig. 2. The intimal area in the diphenhydramine- and cimetidine-treated groups was 1.1 ± 0.3 and 5.5 ± 1.9 ($\times 10^{-3}$ mm^2), respectively, with the value in the diphenhydramine-treated group being significantly ($P < 0.01$) lower than that in the control group, which was 6.2 ± 1.4 ($\times 10^{-3}$ mm^2, Fig. 2A). The ratio of the intimal area to the medial area in the diphenhydramine- and cimetidine-treated groups was 0.11 ± 0.03 and 0.74 ± 0.32, respectively; the value in the diphenhydramine-treated group was significantly ($P < 0.01$) lower than that in the control group (0.64 ± 0.19, Fig. 2C). The medial areas of the diphenhydramine- and cimetidine-treated groups were almost the same as those of the control group (Fig. 2B), showing no significant differences among the groups.

3.2. Effects of histamine receptor antagonists on mouse vascular smooth muscle cell migration and proliferation stimulated by PDGF

PDGF (10 ng/ml) increased the incorporation of [^{3}H]thymidine in mouse vascular smooth muscle cells and

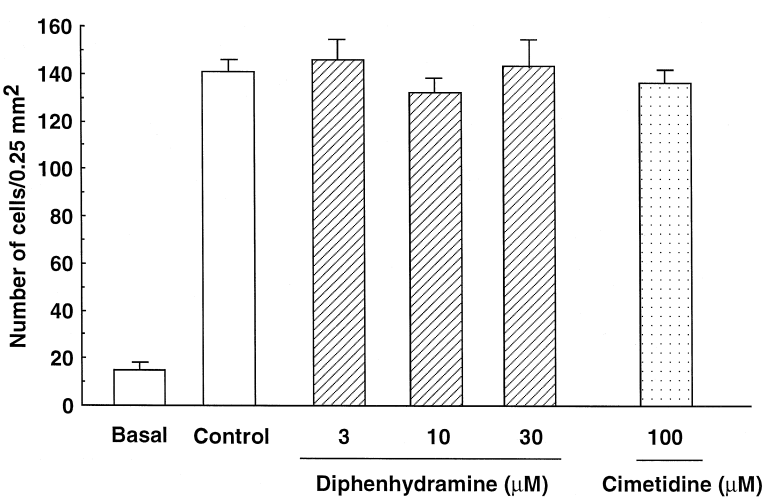

Fig. 3. Effects of diphenhydramine (hatched columns) and cimetidine (dotted columns) on the migration of mouse vascular smooth muscle cells stimulated by PDGF. Data represent means ± S.E.M. values ($n = 8$). Basal: PDGF was not added to the medium. Control: PDGF (10 ng/ml) alone was added to the medium.

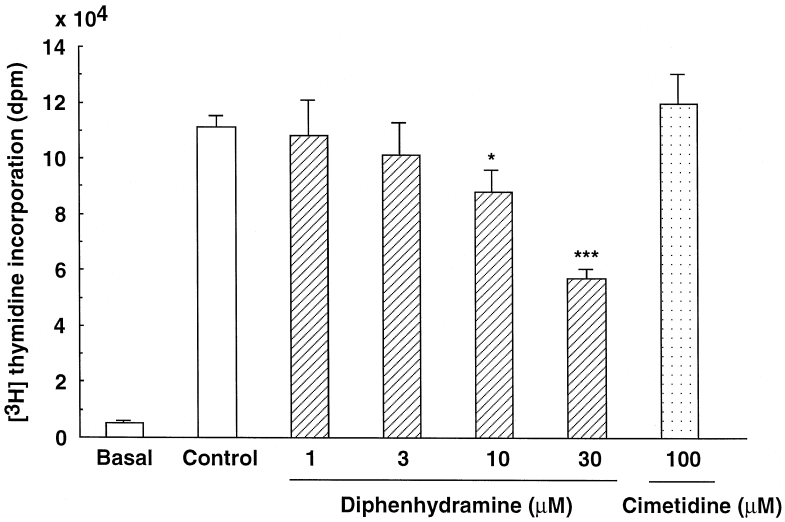

Fig. 4. Effects of diphenhydramine (hatched column) and cimetidine (dotted column) on the incorporation of [^{3}H]-thymidine into mouse vascular smooth muscle cells stimulated by PDGF. Data represent as means ± S.E.M. values ($n = 7$). Basal: PDGF was not added to the medium. Control: PDGF (10 ng/ml) alone was added to the medium. $***P < 0.001$ and $*P < 0.05$ vs. control.

their migration by 20- and 10-fold compared with baseline values before PDGF treatment, respectively. A histamine H_1 receptor antagonist, diphenhydramine, inhibited cell proliferation stimulated by PDGF in a dose-dependent manner, but not cell migration (Figs. 3 and 4). Diphenhydramine at a dose of 30 μM significantly ($P < 0.001$) reduced the incorporation of [^{3}H]thymidine by 50% compared with control. A histamine H_2 receptor antagonist, cimetidine, did not inhibit either the migration or the proliferation stimulated by PDGF (Figs. 3 and 4).

4. Discussion

This model non-mechanically induces endothelial cell injury by a photochemical reaction between green light irradiation and rose bengal. Photo-excitation of rose bengal by green light-generated singlet oxygen causes endothelial injury followed by platelet adhesion, aggregation and the formation of a platelet-rich thrombus at the site of the photochemical reaction (Saniabadi, 1994). In this model, several platelet factors or growth factors including PDGF, transforming growth factor β, and basic fibroblast growth factor, noradrenaline, adenosine 5′-diphosphate, serotonin and histamine are released from adherent platelets, infiltrated leukocytes and injured endothelium, and thus these factors may play a key role in intimal thickening, which mainly consists of smooth muscle cells and extracellular matrix.

In this study, the histamine H_2 receptor antagonist, cimetidine, did not affect intimal thickening after endothelial injury in the mouse femoral artery. The dose of cimetidine used in this study was 200 mg/kg/day, which is comparable to the dose which decreases the size of a gastric ulcer induced by acetic acid when orally administered to rats (Ito et al., 1995). Furthermore, at the same dose, cimetidine inhibited the in vivo growth of human colon cancer stimulated by histamine in the mouse (Adams et al., 1994). Our result is consistent with data reported by Low et al. (1996), who demonstrated that cimetidine at a dose of 350 mg/kg/day did not reduce intimal thickening in the balloon injury model of rat carotid arteries.

There have been few studies of the effects of histamine H_1 receptor antagonists on intimal thickening in vivo. In this study, we demonstrated that a histamine H_1 receptor antagonist, diphenhydramine, markedly reduced intimal thickening in mouse femoral arteries. The dose used in this study was 30 mg/kg/day and is comparable to that causing stet active cutaneous anaphylaxis in mice (Inagaki et al., 1992). The intimal area in animals treated with diphenhydramine was decreased 82% compared with that in control group. Histamine also induces the recruitment of rolling leukocytes, which is mediated by adhesion molecule P-selectin expression on the endothelial cell surface and is a key step in the transmigration of leukocytes into the subendothelium of arteries. Diphenhydramine, but not cimetidine, inhibits P-selectin expression induced by histamine and prevents the histamine-induced recruitment of rolling leukocytes (Asako et al., 1994; Eppihimer et al., 1996). We reported that *myo*-inositol hexaphosphate, a P-selectin and L-selectin inhibitor, inhibited intimal thickening in the same endothelial injury model via the inhibition of leukocyte infiltration (Shimazawa et al., 1997). Thus diphenhydramine may inhibit the infiltration of leukocytes into the arterial wall and reduce the release of growth factors including PDGF, transforming growth factor β and basic fibroblast growth factor from the infiltrated leukocytes. Further studies are needed to clarify the role of histamine in intimal thickening.

PDGF is widely accepted to be involved in intimal thickening after coronary angioplasty. Therefore, we investigated if histamine receptor antagonists had a direct effect on mouse smooth muscle cell migration and proliferation stimulated by PDGF. Cimetidine inhibited neither the migration nor the proliferation stimulated by PDGF. In contrast, diphenhydramine inhibited cell proliferation, but did not inhibit the migration. Based on previous reports (Glazko and Dill, 1949; Yeh, 1986), the blood concentration of diphenhydramine in this study was about 10 μM. These findings suggest that diphenhydramine may reduce intimal thickening, at least in part due to inhibition of cell proliferation stimulated by PDGF. In this study, histamine alone did not cause proliferation and migration of cultured mouse smooth muscle cells (data not shown). Bottaro et al. and Bell and Madri reported that histamine induced the migration of bovine aortic smooth muscle cells, and Bell and Madri demonstrated that the migration induced by histamine was inhibited by cimetidine, but not by diphenhydramine. The difference between our results and the data reported by Bottaro et al. and Bell and Madri may be caused by different species. Histamine is reported to amplify the proliferation stimulated by PDGF in vascular smooth muscle cells (Crowley et al., 1994). PDGF concentrations may increase at the site of injury because PDGF is released from adherent platelets, infiltrated leukocytes and injured endothelium. It has been reported that PDGF stimulates the expression of histamine H_1 receptor mRNA (Takagishi et al., 1995). Consequently, the proliferation stimulated by PDGF may be amplified by histamine via the induction of histamine H_1 receptors.

In conclusion, this study indicates that a histamine H_1 receptor antagonist, but not a histamine H_2 receptor antagonist, inhibits intimal thickening. Histamine may play a key role in intimal thickening, in part via histamine H_1 receptors in this model.

Acknowledgements

We thank Dr. I. Kimura, Department of Chemical Pharmacology, Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, for suggestions for the culture of vascular smooth muscle cells derived from mice.

References

Adams, W.J., Lawson, J.A., Morris, D.L., 1994. Cimetidine inhibits in vitro growth of human colon cancer and reverses histamine stimulated in vitro and in vivo growth. Gut 35, 1632–1636.

Asako, H., Kurose, I., Wolf, R., DeFrees, S., Zleng, Z.L., Phillips, M.L., Paulson, J.C., 1994. Role of H_1 receptors and P-selectin in histamine-induced leukocyte rolling and adhesion in postcapillary venules. J. Clin. Invest. 93, 1508–1515.

Bahadori, L., Milder, J., Gold, L., Botney, M., 1995. Active macrophage-associated TGF-beta co-localizes with type I procollagen gene expression in atherosclerotic human pulmonary arteries. Am. J. Pathol. 146, 1140–1149.

Bauters, C., Meurice, T., Hamon, M., McFadden, E., Lablanche, J.M., Bertrand, M.E., 1996. Mechanisms and prevention of restenosis: from experimental models to clinical practice. Cardiovasc. Res. 31, 835–846.

Bell, L., Madri, J.A., 1989. Effect of platelet factors on migration of cultured bovine aortic endothelial and smooth muscle cells. Circ. Res. 65, 1057–1065.

Bottaro, D., Shepro, D., Peterson, S., Hechtman, H.B., 1985. Serotonin, histamine, and norepinephrine mediation of endothelial and vascular smooth muscle cell movement. Am. J. Physiol. 248, C252–C257.

Crowley, S.T., Demosey, E.C., Horwitz, K.B., Horwitz, L.D., 1994. Platelet-induced vascular smooth muscle cell proliferation is modulated by the growth amplification factors serotonin and adenosine diphosphate. Circulation 90, 1908–1918.

Eppihimer, M.J., Wolitzky, B., Anderson, D.C., Labow, M.A., Granger, D.N., 1996. Heterogeneity of expression of E- and P-selectins in vivo. Circ. Res. 79, 560–569.

Glazko, A.J., Dill, W.A., 1949. Biochemical studies on diphenhydramine (Benadryl): II. Distribution in tissues and excretion. J. Biol. Chem. 179, 403–408.

Greisler, H.P., Henderson, S.C., Lam, T.M., 1993. Basic fibroblast growth factor production in vitro by macrophages exposed to Dacron and polyglactin 910. J. Biomater. Sci. Polym. Ed. 4, 415–430.

Inagaki, N., Miura, T., Nagai, H., Koda, A., 1992. Active cutaneous anaphylaxis in the mouse ear. Japan J. Pharmacol. 59, 201–208.

Ito, M., Inaguma, K., Suzuki, Y., Segami, T., Suzuki, Y., 1995. Healing-promoting action of the zinc–cimetidine complex on acetic acid-induced gastric ulcers in rats. Japan J. Pharmacol. 68, 287–295.

Kaartinen, M., Penttila, A., Kovanen, P.T., 1996a. Mast cells in rupture-prone areas of human coronary atheromas produce and store TNF-alpha. Circulation 94, 2787–2792.

Kaartinen, M., Penttila, A., Kovanen, P.T., 1996b. Mast cells accompany microvessels in human coronary atheromas: implications for intimal neovascularization and hemorrhage. Atherosclerosis 123, 123–131.

Kaltenbach, M., Kober, G., Schere, D., Vallbracht, C., 1985. Recurrence rate after successful coronary angioplasty. Eur. Heart J. 6, 276–281.

Kikuchi, S., Umemura, K., Kondo, K., Nakashima, M., 1996. Tranilast suppresses intimal hyperplasia after photochemically induced endothelial injury in the rat. Eur. J. Pharmacol. 295, 221–227.

Kikuchi, S., Umemura, K., Kondo, K., Saniabadi, A.R., Nakashima, M., 1998. Photochemically induced endothelial injury in the mouse as a screening model for inhibitors of vascular intimal thickening. Arterioscl. Throm. Vas.

Kobayashi, S., Mimura, Y., Naitoh, T., Kimura, I., Kimura, M., 1993. Chemical structure-activity of cnidium rhizome-derived phthalides for the competence inhibition of proliferation in primary cultures of mouse aorta smooth muscle cells. Jpn. J. Pharmacol. 63, 353–359.

Liu, M.W., Roubin, G.S., King, S.B. III, 1989. Restenosis after coronary angioplasty: potential biologic determinant and role of intimal hyperplasia. Circulation 79, 1374–1387.

Low, J.D., House, A.K., Norman, P.E., 1996. Role of cimetidine in the prevention of intimal hyperplasia in rat carotid artery. Br. J. Surg. 83, 72–74.

Mannaioni, P.F., Di Bello, M.G., Masini, E., 1997. Platelets and inflammation: role of platelet-derived growth factor, adhesion molecules and histamine. Inflamm. Res. 46, 4–18.

Metzler, B., Xu, Q., 1997. The role of mast cells in atherosclerosis. Int. Arch. Allergy Immunol. 114, 10–14.

Miyazawa, N., Umemura, K., Kondo, K., Nakashima, M., 1997. Effects of pemirolast and tranilast on intimal thickening after arterial injury in the rat. J. Cardiovasc. Pharmacol. 30, 157–162.

Morisaki, N., Koyama, N., Kawano, M., Mori, S., Umemiya, K., Koshikawa, T., Saito, Y., Yoshida, S., 1992. Human macrophages

modulate the phenotype of cultured rabbit aortic smooth muscle cells through secretion of platelet-derived growth factor. Eur. J. Clin. Invest. 22, 461–468.

Ohsawa, H., Kanai, M., Noike, H., Uchi, T., Yoshinuma, M., Mineoka, K., Hitsumoto, T., Tomioka, H., Fujii, T., Siono, N., Suzuki, N., Tokuhiro, K., 1995. Effects of pemirolast potassium on prevention of angiographic restenosis after percutaneous transluminal coronary angioplasty. Jpn. Circ. J. 59, 390–391.

Ross, R., 1986. The pathogenesis of atherosclerosis: an update. N. Eng. J. Med. 314, 488–500.

Ross, R., 1993. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 362, 801–809.

Saniabadi, A.R., 1994. Photosensitisers and photochemical reactions. In: Nakashima, M. (Ed.), A Novel Photochemical Model for Thrombosis Research and Evaluation of Antithrombotic and Thrombolytic Agents. Churchill Livingstone, London, New York, Tokyo, pp. 1–19.

Shimazawa, M., Watanabe, S., Kondo, K., Mizuno, A., Umemura, K., Nakashima, M., 1997. Neutrophil accumulation mediated by L- or P-selectin promotes intimal hyperplasia in mice. Jpn. J. Pharmacol. 73, 202, (Suppl. 1).

Takagishi, T., Sasaguri, Y., Nakano, R., Arima, N., Tanimoto, A., Fukui, H., Morimatsu, M., 1995. Expression of the histamine H_1 receptor gene in relation to atherosclerosis. Am. J. Pathol. 146, 981–988.

The TREAT study investigators, 1994. The impact of tranilast on restenosis following coronary angioplasty: the Tranilast Restenosis Following Angioplasty Trial (TREAT). Circulation 90, I–652.

Yeh, S.Y., 1986. The effect of antihistaminic drugs on pentazocine antinociception in the rat. Pharmacol. Biochem. Behav. 24, 925–930.