ELSEVIER

European Journal of Pharmacology 331 (1997) 237–243

ejp

Role of mast cell histamine in the formation of rat paw edema: A microdialysis study

Yancai Guo [a], Takatoshi Mochizuki [a,*], Eiichi Morii [b], Yukihiko Kitamura [b], Kazutaka Maeyama [a]

[a] *Department of Pharmacology, Ehime University School of Medicine, Shigenobu-cho, Onsen-gun, Ehime 791-02, Japan*
[b] *Department of Pathology, Faculty of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka 565, Japan*

Received 14 April 1997; revised 9 May 1997; accepted 12 May 1997

Abstract

We determined the endogenous histamine concentration in the subplantar space of rat hind paws using an in vivo microdialysis technique. A microdialysis probe was implanted into the rat hind paw and the histamine content in dialysates was measured by high performance liquid chromatography–fluorometry. In wild type (+/+) rats, the histamine output (basal level 25.7 ± 0.9 pmol/ml) increased 115-, 199- and 426-fold rapidly after subplantar injection of compound 48/80 at doses of 0.5, 5 and 50 μg/paw, respectively. In genetically mast cell-deficient (Ws/Ws) rats, the basal level of histamine was one third of that obtained from +/+ rats, and was not increased by compound 48/80 injection. With this treatment, marked, dose dependent, but relatively gradual development of the paw edema was found in +/+ rats. However, no edema formation was observed in Ws/Ws rats. Histological observations showed neither mast cells nor edema to be present in the paw skin of Ws/Ws rats. These findings indicate the critical role of histamine as a trigger for the development of edema in vivo. In addition, Ws/Ws rats will provide important information as to the roles of mast cells in the inflammatory response. © 1997 Elsevier Science B.V.

Keywords: Microdialysis; Histamine; Paw edema; Mast cell deficient rat (Ws/Ws rat); Compound 48/80; Degranulation

1. Introduction

Connective tissue-type mast cells are one of the major sources of histamine. Their degranulation is caused by antigen challenge mediated via immunoglobulin E, and also by non-immunologic secretagogues like substance P (Hua et al., 1996), neurokinin A (Joos and Pauwels, 1993), extracellular ATP (Sudo et al., 1996) and so on, which result in rapid and marked histamine release (Pearce, 1989). Histamine induces anaphylactic responses such as vasodilation, increased vascular permeability and contraction of smooth muscles. Thus, mast cells may play some important roles in diverse immunological and pathological processes (Wershil and Galli, 1994).

Compound 48/80 is known as a potent inducer of degranulation and of the release, from connective tissue-type mast cells, of histamine and other chemical mediators which are responsible for anaphylactic symptoms. One of the well used approaches in the examination of the immunopathological mechanisms of anaphylactic and inflammatory disorders is to elicit the formation of paw edema by injecting various substances into the subplantar tissue of rats and mice (Antunes et al., 1990; Giraldelo et al., 1994; Lloret and Moreno, 1994; Wang et al., 1994; Amann et al., 1995; Sautebin et al., 1995). There are, however, only a limited number of studies showing changes in the concentrations of such chemical mediators at the site of elicited inflammation in vivo.

An in vivo microdialysis technique has been widely used in the measurement of the extracellular concentration of endogenous substances (Ungerstedt, 1984). This technique is mainly used to determine the concentration of molecules in the brain, and we have used this method previously to measure neuronal histamine and acetylcholine release from the rat brain (Mochizuki et al., 1991; Mochizuki et al., 1994). A variety of types of dialysis probes have been available, enabling us to monitor the dynamics of histamine in peripheral tissues such as rat

* Corresponding author. Tel.: (81-89) 960-5260; Fax: (81-89) 960-5263.

PII S0014-2999(97)01002-9

blood (Sakurai et al., 1993), guinea-pig skin (Okahara et al., 1995) and human skin (Horsmanheimo et al., 1996; Petersen et al., 1996), related to the physiological and pathophysiological events in situ.

In the present study, we measured endogenous histamine levels in the subplantar space of the rat hind paw using a microdialysis technique coupled with high performance liquid chromatography (HPLC)-fluorometry. We determined the effect of compound 48/80 on histamine release and edema formation. In addition, we performed the same experiments using mast cell-deficient (Ws/Ws) rats, recently discovered by Niwa et al. (1991). Comparison of these results from wild type and Ws/Ws rats will provide us with important information as to the roles of mast cells in anaphylactic and inflammatory responses.

2. Materials and methods

The animal experiments performed in the present study were conducted according to the guidelines of the Animal Care Committee of Ehime University School of Medicine, and the experimental protocols were approved by the Committee.

2.1. Animals

Male Ws/Ws rats deficient in mast cells and normal (+/+) rats, both groups weighing 180–230 g, were used. They were bred in our laboratory as described by Niwa et al. (1991). They were housed at a constant temperature (22 ± 2°C) with a constant relative humidity (55 ± 10%) on an automatically controlled 12:12 h light–dark cycle (lights on at 7.00 a.m.) and had free access to food and water.

2.2. Microdialysis procedure in the rat hind paw

The rats were anaesthetized with urethane (1.2 g/kg, i.p.) and placed on their backs. The body temperature was kept at 37°C with a warming light. Either of the hind paws was fixed tightly on a platform, and a dummy needle covered with the guide tubing for the microdialysis probe was inserted into the subcutaneous space of the plantar area. After the dummy needle was removed from the tubing, the microdialysis probe (CMA/20, membrane length 4 mm; Carnegie Medicin, Stockholm, Sweden) was inserted through the tubing into the tissue. Then, the tubing was torn apart to expose the membrane surface to the subcutaneous tissue. The area was perfused with saline at a flow rate of 2 μl/min. Under these conditions, the recovery of histamine from the surrounding fluid in the dialysate (relative recovery) was 14 ± 0.8% (means ± S.E.M., $n = 6$) as estimated by an in vitro perfusion test, in which the probe was placed in a test tube containing a 10 μM standard solution of histamine and was perfused at 37°C. The dialysate was collected every 20 min for up to 8 h, and was kept at −20°C until histamine determination. Either compound 48/80 (Sigma, St. Louis, MO, USA), at doses of 0.5, 5 and 50 μg dissolved in 50 μl saline or the same volume of saline was injected into the subcutaneous space near the dialysis site (approximately 2 mm beside the dialysis membrane) 3 h after insertion of the probe. At the end of each experiment, the skin of both hind paws, one treated and the other untreated, was removed and frozen at −20°C for determination of the histamine content.

In some experiments, the histamine concentration in the dialysates of whole blood and the hind paws were monitored simultaneously by the microdialysis technique in vivo. The detailed method was described by Sakurai et al. (1993). Briefly, the pectoral muscle of an anaesthetized rat was exposed, and a guide cannula was inserted into the jugular vein through the muscle. A microdialysis probe (CMA/10, membrane length 10 mm; Carnegie Medicin) was introduced into the guide, and perfused with saline at a flow rate of 2 μl/min (the relative recovery; 23 ± 1.2%, $n = 6$). Dialysate was collected every 20 min, and kept at −20°C until histamine determination.

2.3. Determination of histamine by HPLC-fluorometry

Histamine content in the dialysate and the tissue homogenate was determined by an HPLC-fluorometry technique established by Yamatodani et al. (1985). Each 40 μl of dialysate was diluted 5 times with 5 mM Na_2EDTA, and 50 μl of the sample was injected directly into a column packed with cation exchanger, TSKgel SP2SW (150×6 mm i.d.; Tosoh, Tokyo, Japan). The histamine eluted with 0.25 M potassium phosphate at a flow rate of 0.6 ml/min was post-labeled with *o*-phthalaldehyde and detected fluorometrically in an F1080 fluorometer (Hitachi, Tokyo, Japan) using excitation and emission wavelengths of 360 and 450 nm, respectively. Paw skins were washed with cold saline, blotted with filter paper, weighed, and promptly homogenized in 1 ml of 3% perchloric acid with a polytron homogenizer operated at maximal speed in an ice bath. The homogenate was centrifuged at $10\,000 \times g$ for 10 min at 4°C, and 50 μl of the supernatant was subjected to HPLC-fluorometry.

2.4. Measurement of paw edema

Using separate animals, we examined the development of edema in the hind paw by the method of weight displacement (Newbold and Brain, 1993). Rats were under light ether anaesthesia for the following manipulations of injection and measurement. First, the baseline weights were measured for each hind paw by dipping them up to a fixed level in a beaker containing water. The beaker, positioned on a top pan balance (AE 240, Mettler-Toledo, Switzerland), was calibrated to zero before each measure-

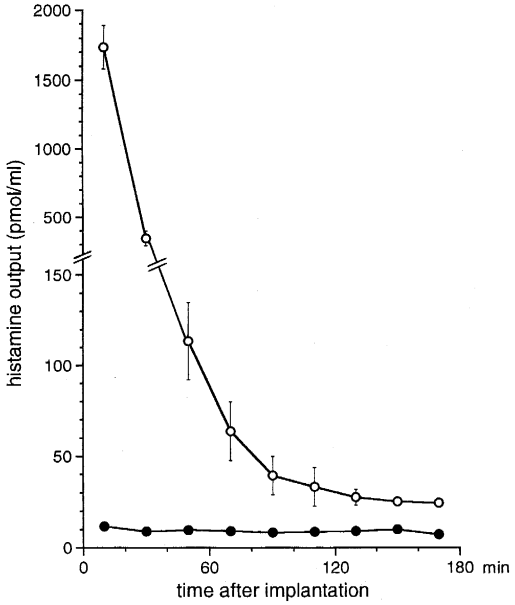

Fig. 1. Histamine output after implantation of a microdialysis probe in the paws of normal +/+ (○) and Ws/Ws (●) rats. The values are means ± S.E.M. ($n = 4$).

ment. Then, either 0.5, 5 and 50 μg of compound 48/80 or saline was injected into one of the hind paws subplantarly. Hind paws from both sides, one as the treated side and the other as the control, were reweighed after injection at the times indicated. The increased volume (Δ ml) of the paw caused by swelling was estimated by calculating the difference between the weight at a particular time and the initial weight.

2.5. Histological observation

Paw skin pieces of +/+ and Ws/Ws rats were removed 4 h after injection of 50 μg of compound 48/80 or saline, fixed in Carnoy's solution and embedded in paraffin. Paraffin sections were cut 4 μm thick and stained with alcian blue. Mast cells in the paw skin were examined under a light microscope (magnification ×760).

2.6. Statistical analysis

For the microdialysis data, histamine output was observed to be stable 2 h after implantation of the probe. Thus, the mean value of histamine output observed during the next 1 h was defined as the basal output and the subsequent fractions were expressed as percentages of this value, except for those in Fig. 1, in which absolute values were used to show the actual time-course change in histamine output after the implantation. Histamine content in the paw skin was expressed as nmol/g wet tissue weight. The statistical significance was determined by one-way analysis of variance followed by Fisher's PLSD test. Probability values of < 0.05 were considered significant.

3. Results

3.1. Determination of the basal histamine level in the subplantar space of hind paws

Fig. 1 shows the time-course of changes in histamine output in the subplantar space of hind paws after implantation of the microdialysis probe. For +/+ rats, the histamine level was quite high, especially just after implantation (1.73 ± 0.15 nmol/ml), but declined to a stable level within 2 h. The mean histamine output estimated during the next 1 h was 25.7 ± 0.9 pmol/ml, a value which we took as the basal output value of histamine. In subsequent experiments, dialysates obtained during the first 2 h after the implantation were discarded. In Ws/Ws rats, however, no drastic change in histamine level was observed even just after implantation. Histamine output seemed stable over the observation period. The basal output was esti-

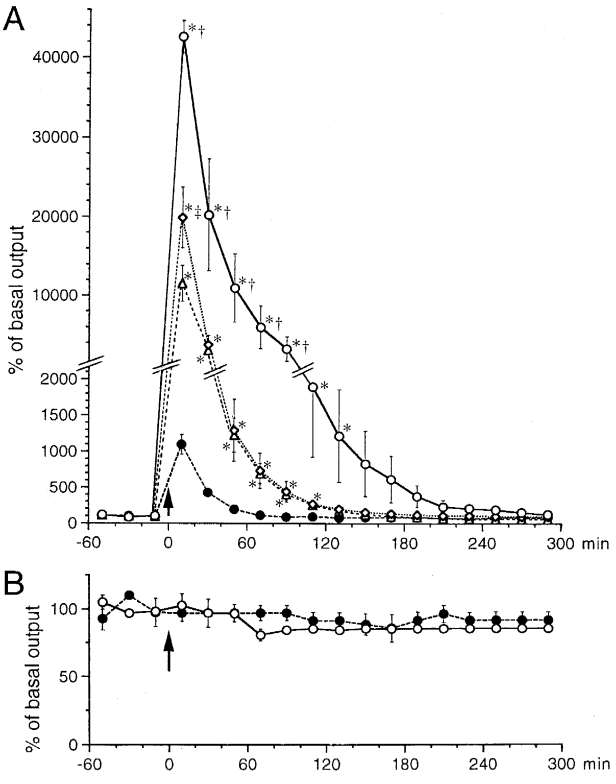

Fig. 2. Changes in histamine output from the paws of +/+ (A) and Ws/Ws (B) rats after subplantar injection of compound 48/80. The average of the first three fractions (basal release) is 25.7 ± 0.9 pmol/ml in +/+ rat (A) and 8.8 ± 0.8 pmol/ml in Ws/Ws rat (B). The data are expressed as percentages of the basal release (mean ± S.E.M.). (A) Compound 48/80, at doses of 0.5 (△, $n = 4$), 5 (◇, $n = 4$) and 50 (○, $n = 5$) μg dissolved in 50 μl of saline, or the same volume of saline (●, $n = 5$) was injected after the collection of the first three fractions as indicated by an arrow. (B) Compound 48/80, at a dose of 50 (○, $n = 4$) μg, or saline (●, $n = 4$) was injected as indicated by an arrow. * $P < 0.05$, compared to saline-treated group. † $P < 0.05$, compared to compound 48/80 (0.5 and 5 μg)-treated group. ¬ d $P < 0.05$, compared to compound 48/80 (0.5 μg)-treated group.

Table 1
Histamine contents in the hind paws of +/+ and Ws/Ws rats 5 h after compound 48/80 and saline treatment

	+/+ rats		Ws/Ws rats	
	Injected side	Control side	Injected side	Control side
Saline 50 μl	61.49 ± 2.66	80.26 ± 6.06	0.23 ± 0.04	0.21 ± 0.03
Compound 48/80 50 μg/50 μl saline	9.96 ± 0.83 [a,b]	86.15 ± 11.14	0.32 ± 0.08	0.34 ± 0.11

Data are means ± S.E.M. ($n = 5$), in nmol/g wet tissue weight.
[a] $P < 0.05$, compared to the control side.
[b] $P < 0.05$, compared to the injected side of saline-treated group.

mated at 8.8 ± 0.8 pmol/ml, which was one third of that obtained from +/+ rats. On the basis of our in vitro recovery test, histamine concentrations in the subplantar space of +/+ and Ws/Ws rats were about 183.6 and 57.1 nM, respectively.

3.2. Effect of compound 48/80 on histamine release

Fig. 2A shows the effect of subplantar injection of compound 48/80 on histamine output in +/+ rats. Compound 48/80, at a dose of 0.5 μg, induced a 115-fold increase in histamine release compared with the basal level soon after the injection. The histamine release, then, declined monoexponentially to the basal level in 3 h. The effect of compound 48/80 was dose-dependent; 5 and 50 μg of compound 48/80 caused 199- and 426-fold increases in histamine release, respectively. The injection of saline alone, however, induced only an 11-fold increase in histamine release, which returned to the basal level within 1 h. In some animals, the histamine concentration in the blood and that in the subplantar space were monitored simultaneously. The basal concentration of histamine in the blood was 38.2 ± 4.6 pmol/ml (166.1 nM, estimated from the in vitro recovery rate) and increased 2.2-fold after the subplantar injection of 50 μg compound 48/80. The histamine concentration returned to its basal level within 1 h (data not shown).

In Ws/Ws rats, as shown in Fig. 2B, no histamine release was induced by the subplantar injection of either compound 48/80 (50 μg) or saline. Histamine output was stable throughout the observed period.

3.3. Histamine content in paw skins

Table 1 shows the histamine content in the paw skins from both the compound 48/80, 50 μg-injected, or saline-injected (also probe-implanted) side, and the contralateral untreated side (control side) 5 h after the injection. In +/+ rats, the combination of probe implantation and saline injection caused a decrease in histamine content in the injected side (61.49 nmol/g), compared with the control side (80.20 nmol/g). In the compound 48/80-injected paw skins, the histamine content was 9.96 nmol/g, which was markedly less than that in the control side (86.15 nmol/g). However, in Ws/Ws rats, no pronounced difference in the histamine content was observed between the compound 48/80-injected side and control side (0.32 and 0.34 nmol/g, respectively), or the saline-injected side and control side (0.23 and 0.21 nmol/g, respectively).

3.4. Paw edema

Fig. 3A shows the time-course of the development of the paw edema elicited by subplantar injections in the various animals. In normal +/+ rats, paw edema developed rapidly after compound 48/80 treatment at a dose of 0.5 μg, and reached a maximum 2 h after the injection. Significant swelling was observed up to 5 h and disappeared completely after 24 h. The larger doses of compound 48/80 (5 and 50 μg) caused more marked development of the edema, whereas a transient, small swelling was found in saline treated +/+ rats. As shown in Fig. 3B,

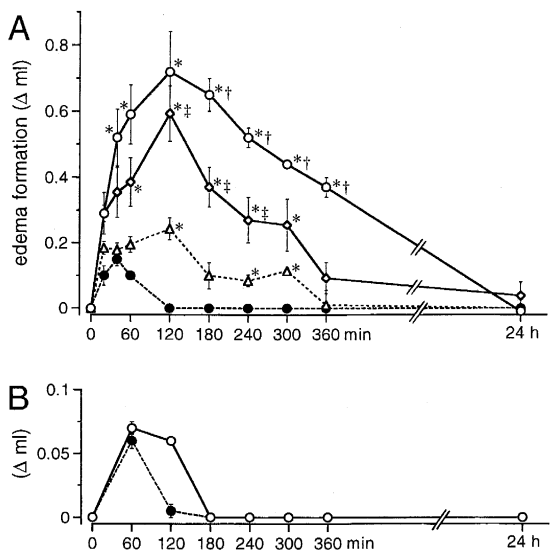

Fig. 3. Time-course of the development of paw edema in +/+ (A) and Ws/Ws (B) rats elicited by subplantar injection of compound 48/80. The edema was expressed as the increased volume (Δ ml, mean ± S.E.M.). (A) Compound 48/80, at doses of 0.5 (△, $n = 4$), 5 (◇, $n = 4$) and 50 (○, $n = 5$) μg, or saline (●, $n = 3$) was injected at 0 min. (B) Compound 48/80, at a dose of 50 (○, $n = 3$) μg, or saline (●, $n = 3$) was injected at 0 min. * $P < 0.05$, compared to saline-treated group. † $P < 0.05$, compared to compound 48/80 (0.5 and 5 μg)-treated group. ¬ d $P < 0.05$, compared to compound 48/80 (0.5 μg)-treated group.

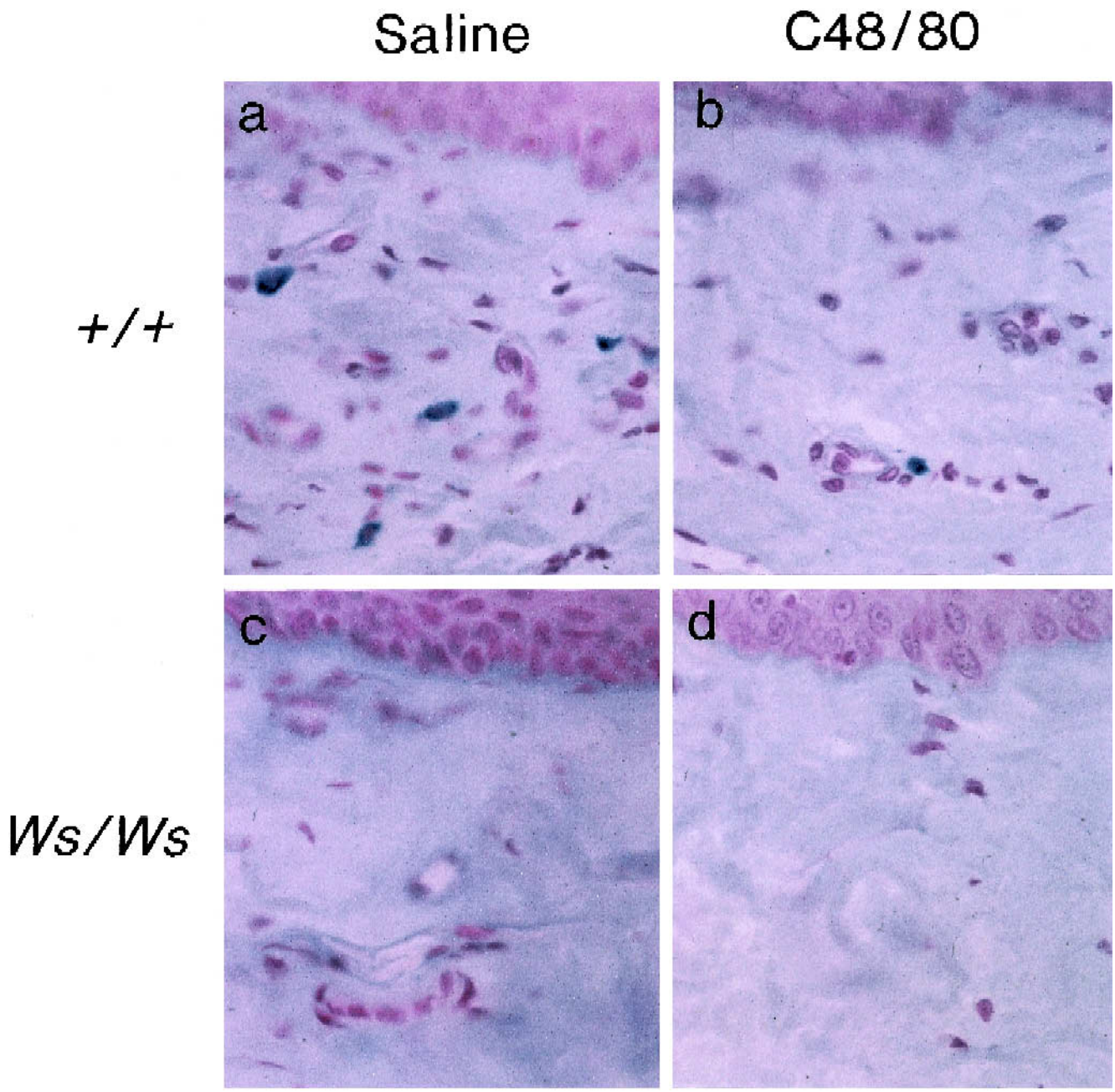

Fig. 4. Representative photographs of paw sections stained with alcian blue in + / + and Ws/Ws rats 4 h after injection of 50 μg of compound 48/80 or saline. (a) + / + rat treated with 50 μl of saline, (b) + / + rat treated with 50 μg of compound 48/80 dissolved in 50 μl of saline, (c) Ws/Ws rat treated with saline, (d) Ws/Ws rat treated with 50 μg of compound 48/80.

however, there was almost no edema elicited either by compound 48/80 (50 μg) or saline treatment in Ws/Ws rats. In all the experiments, the volume of the contralateral (untreated) paw was also measured, and no swelling was observed (data not shown).

3.5. Histological observations

Mast cells in the paw skin stained with alcian blue are shown in Fig. 4. In the dermis of + / + rats treated with saline (Fig. 4a), mast cells were stained with alcian blue, but the number of stained mast cells decreased and extracellular space was edematous after compound 48/80 treatment (50 μg, Fig. 4b). In Ws/Ws rats, no mast cells were detected in the dermis (Fig. 4c) and the extracellular matrix was not changed after treatment with compound 48/80 (50 μg, Fig. 4d).

4. Discussion

The Ws/Ws rats discovered by Kitamura and his colleagues are devoid of connective tissue-type mast cells,

because of the deletion of 12 nucleotide bases in the tyrosine kinase domain of the c-*kit* receptor gene (Tsujimura et al., 1991). Histamine content and the number of alcian blue positive mast cells in the skin of Ws/Ws rats were both less than 0.3% of those in +/+ rats later than 10 weeks after birth. This indicates that histamine in the skin appears to derive from mast cells (Onoue et al., 1993). It is expected that results from mutant rats would be very useful for determining the function of mast cells when compared with results from congenic, +/+ rats (Sugimoto et al., 1995). In the present study, we observed a marked induction by compound 48/80 of histamine release in the subplantar space of the hind paw only in +/+ rats (Fig. 2A). The subplantar injection of the compound 48/80 acted mainly on mast cells present in the subcutaneous tissue around the injection site, because only a 2-fold increase in blood histamine concentration was observed after the injection, suggesting that the increased histamine was not derived from other peripheral tissues transported in by the circulation. This idea gained support from the observation of a large decrease in histamine content in the skin (Table 1) and a clear development of edema (Fig. 3A) only in the paws of the compound 48/80-treated side in +/+ rats. For Ws/Ws rats, neither an increase in histamine release (Fig. 2B), nor a decrease in histamine content in the skin (Table 1), nor the development of edema (Fig. 3B) were found after compound 48/80 injection. Thus we can conclude that specific histamine release, caused by degranulation of local mast cells, induced the development of the paw edema in +/+ rats.

The histamine level in subplantar dialysates of Ws/Ws rats was one third of that of +/+ rats. This level must reflect the amount of histamine from non-mast cell origin, such as basophils and enterochromaffin-like cells, because, as shown in Fig. 4, there are no mast cells in the subplantar tissue of Ws/Ws rats. It is noteworthy that there was no change in histamine levels in Ws/Ws rats while a more than 60-fold increase in histamine release was found in +/+ rats soon after the implantation (Fig. 1). This may suggest that local tissue damage, or adverse stimuli such as pain, induced the release of histamine from mast cells. Similar results found in +/+ rats were that the subplantar injection of saline elicited an 11-fold increase in histamine release (Fig. 2A), transient swelling (Fig. 3A) and a small loss of histamine content in the skin of the treated paw (Table 1). We also found that a mere prick with the injection needle without saline infusion caused a 2-fold increase in histamine release in +/+ rats (data not shown). These results suggest that sensory stimuli are involved in activating histamine release from mast cells. Previous reports support the idea of an interaction between mast cells and sensory nerves (C-fibers). Mast cells are in direct anatomical contact with neuropeptide-containing sensory nerves, and electrical stimulation of nerve fibers induces mast cell degranulation (Gazelius et al., 1981; Dimitriadou et al., 1991). In addition, neuropeptides such as substance P and neurokinin A, released from sensory nerve terminals, have been suggested to stimulate histamine release from mast cells (Joos and Pauwels, 1993; Horsmanheimo et al., 1996; Hua et al., 1996). This system is suspected to be one of the mechanisms underlying inflammatory disorders caused by the central nervous system (Harvima et al., 1994). The present results were consistent with these findings, however no histamine increase, as determined by microdialysis, was observed in the subcutaneous space of guinea pig dorsal skin after intracutaneous injection of saline (20 μl) (Okahara et al., 1995). There might be some difference in the anatomical structure of sensory nerve innervation and in mast cell distribution between the paws and the dorsal skin. Further studies will be necessary to clarify the effect of sensory stimuli on histamine release and the inflammatory response.

Comparing the time-course of the change in histamine release (Fig. 2A) with that of the development of edema (Fig. 3A) after compound 48/80 injection into +/+ rats, it is clear that the edema developed more gradually. Although the edema was elicited soon after the injection, it reached its maximal volume 2 h after the injection, when the histamine output was already submaximal and came close to the basal levels. The result indicates that histamine promoted the increase in vascular permeability immediately after being released from the mast cells and caused the subsequent swelling process. The compound 48/80-induced edema formation was abolished by pretreatment of the animals with H_1-receptor antagonists (Blazsó and Gábor, 1994), and in our preliminary study, the edema was not elicited by compound 48/80, at a dose of 5 μg, with pretreatment with the H_1-antagonist, chlorpheniramine (10 mg/kg, p.o.), which was administered 1 h prior to compound 48/80 injection (data not shown). With this in mind, we suppose that histamine in the tissue is important as a trigger, especially in the initial phase of eliciting edema, but may be metabolized or removed from the site of the elicited inflammation rapidly by the circulation, whereas the gap formation by endothelial cells would persist longer than the metabolism of histamine. Alternatively, we suppose that the full development of edema may require other mediators besides histamine. It is well known that when mast cells are activated, serotonin or other granule contents are released immediately (Maling et al., 1974), membrane-derived lipid mediators, such as prostaglandins and leukotrienes are synthesized in minutes and finally a number of cytokines, including tumor necrosis factor (TNF-α) and interleukins, are produced for several hours (Walsh et al., 1991). These preformed and newly formed mediators may play important roles in inflammatory disorders. In the present study, no increase in histamine release and no edema formation were observed after compound 48/80 injection into Ws/Ws rats because of the lack of mast cells. Therefore, a good way to characterize different inflammation-promoting substances

in vivo might be to apply them to Ws/Ws rats and to observe inflammatory responses such as edema formation. Such studies might clarify the contribution of mast cells in inflammatory disorders.

In conclusion, we would like to emphasize that (1) the present method, measuring histamine in the subplantar tissue by microdialysis, is adaptable to further studies on allergic and inflammatory disorders, and (2) genetically mast cell-deficient Ws/Ws rats are useful and well-suited for the investigation of the pathophysiological roles of mast cells.

Acknowledgements

This study was partly supported by Grants-in-Aid from the Ministry of Education, Culture and Science of Japan (no. 07557011) and the Fujii Memorial Fund for Asian-Pacific Medical Exchange, Japan.

References

Amann, R., Schuligoi, R., Lanz, I., Donnerer, J., 1995. Histamine-induced edema in the rat paw – effect of capsaicin denervation and a CGRP receptor antagonist. Eur. J. Pharmacol. 279, 227.

Antunes, E., Mariano, M., Cirino, G., Levi, S., De Nucei, G., 1990. Pharmacological characterization of polycation-induced rat hind-paw oedema. Br. J. Pharmacol. 101, 986.

Blazsó, G., Gábor, M., 1994. Anti-oedematous action of some H_1-receptor antagonists. Agents Actions 42, 13.

Dimitriadou, V., Buzzi, M.G., Moskowitz, M.A., Theoharides, T.C., 1991. Trigeminal sensory fiber stimulation induces morphological changes reflecting secretion in rat dura mater mast cells. Neuroscience 44, 97.

Gazelius, B., Brodin, E., Olgart, L., Panopoulos, P., 1981. Evidence that substance P is a mediator of antidromic vasodilatation using somatostatin as a release inhibitor. Acta Physiol. Scand. 113, 155.

Giraldelo, C.M.M., Zappellini, A., Muscara, M.N., De Luca, I.M.S., Hyslop, S., Cirino, G., Zatz, R., De Nucci, G., Antunes, E., 1994. Effect of arginine analogues on rat hind paw oedema and mast cell activation in vitro. Eur. J. Pharmacol. 257, 87.

Harvima, I.T., Horsmanheimo, L., Naukkarinen, A., Horsmanheimo, M., 1994. Mast cell proteinases and cytokines in skin inflammation. Arch. Dermatol. Res. 287, 61.

Horsmanheimo, L., Harvima, I.T., Harvima, R.J., Ylonen, J., Naukkarinen, A., Horsmanheimo, M., 1996. Histamine release in skin monitored with the microdialysis technique does not correlate with the weal size induced by cow allergen. Br. J. Dermatol. 134, 94.

Hua, X.Y., Back, S.M., Tam, E.K., 1996. Substance P enhances electrical field stimulation-induced mast cell degranulation in rat trachea. Am. J. Physiol. 270, L985.

Joos, G.F., Pauwels, R.A., 1993. The in vivo effect of tachykinins on airway mast cells of the rat. Am. Rev. Respir. Dis. 148, 922.

Lloret, S., Moreno, J.J., 1994. Effect of nonapeptide fragments of uteroglobin and lipocortin I on oedema and mast cell degranulation. Eur. J. Pharmacol. 264, 379.

Maling, H.M., Webster, M.E., Williams, M.A., Saul, W., Anderson, W. Jr., 1974. Inflammation induced by histamine, serotonin, bradykinin and compound 48/80 in the rat: Antagonists and mechanisms of action. J. Pharmacol. Exp. Ther. 191, 300.

Mochizuki, T., Yamatodani, A., Okakura, K., Takemura, M., Inagaki, N., Wada, H., 1991. In vivo release of neuronal histamine in the hypothalamus of rats measured by microdialysis. Naunyn-Schmiedeberg's Arch. Pharmacol. 343, 190.

Mochizuki, T., Okakura-Mochizuki, K., Horii, A., Yamamoto, Y., Yamatodani, A., 1994. Histaminergic modulation of hippocampal acetylcholine release in vivo. J. Neurochem. 62, 2275.

Newbold, P., Brain, S.D., 1993. The modulation of inflammatory oedema by calcitonin gene-related peptide. Br. J. Pharmacol. 108, 705.

Niwa, Y., Kasugai, T., Ohno, K., Morimoto, M., Yamazaki, M., Dohmae, K., Nishimune, Y., Kondo, K., Kitamura, Y., 1991. Anemia and mast cell depletion in mutant rats that are homozygous at 'white spotting (Ws)' locus. Blood 78, 1936.

Okahara, K., Murakami, T., Yamamoto, S., Yata, N., 1995. Skin microdialysis: Detection of in vivo histamine release in cutaneous allergic reactions. Skin Pharmacol. 8, 113.

Onoue, H., Maeyama, K., Nomura, S., Kasugai, T., Tei, H., Kim, H.M., Watanabe, T., Kitamura, Y., 1993. Absence of immature mast cells in the skin of Ws/Ws rats with a small deletion at tyrosine kinase domain of the c-kit gene. Am. J. Pathol. 142, 1001.

Pearce, F.L., 1989. Mast cells: Function, differentiation and activation. Curr. Opin. Immunol. 1, 630.

Petersen, L.J., Brasso, K., Pryds, M., Skov, P.S., 1996. Histamine release in intact human skin by monocyte chemoattractant factor-1, RANTES, macrophage inflammatory protein-1α, stem cell factor, anti-IgE, and codeine as determined by an ex vivo skin microdialysis technique. J. Allergy Clin. Immunol. 98, 790.

Sakurai, E., Gunji, E., Iizuka, Y., Hikichi, N., Maeyama, K., Watanabe, T., 1993. In vivo microdialysis measurement of histamine in rat blood effect of compound 48/80 and histamine receptor antagonists. J. Pharmacol. Toxicol. Methods 29, 105.

Sautebin, L., Ialenti, A., Ianaro, A., Di Rosa, M., 1995. Endogenous nitric oxide increases prostaglandin biosynthesis in carrageenin rat paw oedema. Eur. J. Pharmacol. 286, 219.

Sudo, N., Tanaka, K., Koga, Y., Okumura, Y., Kubo, C., Nomoto, K., 1996. Extracellular ATP activates mast cells via a mechanism that is different from the activation induced by the cross-linking of Fc receptors. J. Immunol. 156, 3970.

Sugimoto, K., Maeyama, K., Alam, M.K., Sakurai, E., Onoue, H., Kasugai, T., Kitamura, Y., Watanabe, T., 1995. Brain histaminergic system in mast cell- deficient (Ws/Ws) rats: Histamine content, histamine decarboxylase activity, and effects of (S) α-fluoromethylhistidine. J. Neurochem. 65, 791.

Tsujimura, T., Hirota, S., Nomura, S., Niwa, Y., Yamazaki, M., Tono, T., Morii, E., Kim, H.M., Kondo, K., Nishimune, Y., Kitamura, Y., 1991. Characterization of Ws mutant allele of rats: A 12-base deletion in tyrosine kinase domain of c-kit gene. Blood 78, 1942.

Ungerstedt, U., 1984. Measurement of neurotransmitter release by intracranial dialysis. In: Marsden, C.A. (Ed.), Measurement of Neurotransmitter Release In Vivo. John Wiley&Sons, Chichester, p. 81.

Walsh, L.J., Trinchieri, G., Waldorf, H.A., Whitaker, D., Murphy, G.F., 1991. Human dermal mast cells contain and release tumor necrosis factor a, which induces endothelial leukocyte adhesion molecule 1. Proc. Natl. Acad. Sci. USA 88, 4220.

Wang, J.P., Hsu, M.F., Raung, S.L., Kuo, S.C., 1994. Suppressive effect of 2-phenyl-4-quinolone (YT-1) on hind-paw edema and cutaneous vascular plasma extravasation in mice. Naunyn-Schmiedeberg's Arch. Pharmacol. 349, 324.

Wershil, B.K., Galli, S.J., 1994. The analysis of mast cell function in vivo using mast cell-deficient mice. Adv. Exp. Med. Biol. 347, 39.

Yamatodani, A., Fukuda, H., Wada, H., Iwaeda, T., Watanabe, T., 1985. High-performance liquid chromatographic determination of plasma and brain histamine without previous purification of biological samples: Cation-exchange chromatography coupled with post-column derivatization fluorometry. J. Chromatogr. 344, 115.