Roles of Histamine in Exercise-Induced Fatigue: Favouring Endurance and Protecting against Exhaustion

Fukie Nijijima-Yaoita,^{*a} Masahiro Tsuchiya,^b Hiroshi Ohtsu,^c Kazuhiko Yanai,^d Shunji Sugawara,^e Yasuo Endo,^e and Takeshi Tadano^a

^aDepartment of Pharmacology, Tohoku Pharmaceutical University; 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan; ^bDepartment of Aging and Geriatric Dentistry, Graduate School of Dentistry, Tohoku University; 4-1 Seiryomachi, Aoba-ku, Sendai 980-8575, Japan; ^dDepartment of Pharmacology, Graduate School of Medicine, Tohoku University; ^eDepartment of Molecular Regulation, Graduate School of Dentistry, Tohoku University; 4-1 Seiryomachi, Aoba-ku, Sendai 980-8575, Japan; and ^cDepartment of Applied Quantum Medical Engineering, School of Engineering, Tohoku University; 6-6-01-2 Aoba, Aramaki-aza, Aoba-ku, Sendai 980-8575, Japan.

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Exercise necessitates a large supply of O₂ and nutrients and rapid removal of CO₂ and waste products. Histamine is a regulator of the microcirculation (which performs these exchanges), suggesting a possible involvement of histamine in exercise. Histamine is released from either mast cells or non-mast cells. In the latter, histamine is newly formed *via* the induction of histidine decarboxylase (HDC) in response to an appropriate stimulus, and it is released without being stored. Here, in mice, we examined the role of histamine or HDC induction in exercise. Prolonged walking (PW) (in a cylindrical cage turned electrically) increased HDC mRNA and HDC activity in quadriceps femoris muscles. Mice given a histamine H1-receptor antagonist [fexofenadine (peripherally acting) or pyrilamine (peripherally and centrally acting)] or an irreversible HDC inhibitor (α -fluoromethylhistidine) displayed less PW endurance than control mice. Ranitidine (H2-receptor antagonist) tended to reduce endurance. Other histamine-receptor (H3 and H4) antagonists had no significant effects on endurance. Mice deficient in HDC or histamine H1-receptors displayed markedly less endurance than control mice, and HDC activity in the quadriceps femoris of H1-deficient mice was rapidly elevated by PW. Fexofenadine significantly reduced the muscle levels of nitric oxide (NO) metabolites and glycogen after PW. The results support the ideas that (i) histamine is involved in protecting against exercise-induced fatigue or exhaustion, (ii) histamine exerts its protective effect *via* H1 receptors and the ensuing production of NO in skeletal muscle, and (iii) histamine is provided, at least in part, by HDC induction in skeletal muscles during prolonged exercise.

Key words exercise; histidine decarboxylase; histamine receptor; nitric oxide; skeletal muscle

Although it is common knowledge that during exercise (*i.e.* repeated muscle contraction), there is an increased need for nutrients and O₂ to be supplied to skeletal muscles and for waste metabolites and CO₂ to be removed from them, the detailed mechanisms responsible for the support of such vascular functions remain unclear.

Histamine dilates precapillary arterioles and increases capillary permeability.^{1–3)} Thus, histamine, if provided appropriately within or to skeletal muscles, may help to support the supply of O₂ and nutrients and the removal of CO₂ and waste products. The vasodilating effect of histamine on arterioles is largely induced by stimulation of histamine H1 receptors and the ensuing production of nitric oxide (NO).^{3–5)}

It is widely known that histamine is stored within mast cells and basophils. It is also known that the histamine-forming enzyme, histidine decarboxylase (HDC), is a typical adaptive enzyme induced in response to a variety of stimuli.^{6–10)} The histamine newly formed *via* HDC induction is released without being stored,^{7–11)} and it has been suggested that histamine from this source is involved both in the regulation of the microcirculation^{8,9)} and in anabolic processes during rapid cell growth.⁷⁾

Interestingly, prolonged walking (PW) (or other prolonged physical exercise) induces HDC in mouse skeletal muscles,^{12–15)} and the elevation of HDC activity persists for several hours after the exercise ends.¹⁴⁾ It has also been shown that training decreases the magnitude of the exercise-stimulated HDC induction.^{13,14)} It has also been shown that in humans,

histamine H1 and H2 receptors are involved in mediating post-exercise hyperemia in skeletal muscles and/or post-exercise hypotension.^{16–18)} Therefore, a plausible hypothesis is that histamine may play a role in exercise endurance, possibly by reducing muscle fatigue.

In the present study, on mice, we employed antagonists of histamine receptors, an inhibitor of HDC, and mice deficient either in HDC or in histamine H1 receptors to examine the roles played by histamine and HDC in exercise endurance.

MATERIALS AND METHODS

Animals C57BL/6 mice were purchased from Japan CLEA (Tokyo, Japan). Histamine H1-receptor knockout (H1-KO) mice (C57BL/6 background) were originally produced by Inoue and colleagues.¹⁹⁾ HDC-KO mice (C57BL/6 background) were established by Ohtsu *et al.*²⁰⁾ H1-KO and HDC-KO mice were bred in the laboratory of Sugawara (Department of Molecular Immunology, Graduate School of Dentistry, Tohoku University). The mice (male) used for the present experiments were 7 to 8 weeks old. Body weight of the mice at the time of experiments was about 24 g for the other mice. All mice were allowed standard food pellets (LabMR Stock; Nihon Nosan Inc., Yokohama, Japan) and tap water *ad libitum* in an air-conditioned room at 23±1°C and 55±5% relative humidity with a standard 12 h light and 12 h dark cycle (lights on at 07:00 a.m.). All experiments complied with the Guidelines for Care and Use of Laboratory Animals issued by Tohoku Pharmaceutical

* To whom correspondence should be addressed. e-mail: nijijima@tohoku-pharm.ac.jp

University.

Reagents DL- α -Monofluoromethylhistidine (FMH, an irreversible inhibitor of HDC) was a gift from Dr. Kollonitsch of Merck Sharp and Dohme Research Laboratories (Rahway, NJ, U.S.A.).²¹ Fexofenadine, pyrilamine, ranitidine, and thioperamide were purchased from Sigma Chemical Co. (St. Louis, MO, U.S.A.). Fexofenadine was suspended in saline containing 0.5% Tween 80. All other reagents were dissolved in saline. The above reagents were injected intraperitoneally at 0.1 mL per 10 g body weight. JNJ-777120, which was provided by Johnson & Johnson Pharmaceutical Research and Development, LLC, (San Diego, CA, U.S.A.),²² was suspended in saline and injected intraperitoneally at 0.2 mL per 10 g body weight. In all experiments, saline or vehicle was injected at the same volume and same timing as the solutions of test drugs. The doses employed in the present study were within the ranges widely used in experiments on mice and rats.^{22–25}

Prolonged Walking (PW) and PW-Endurance Forced walking at room temperature ($23 \pm 1^\circ\text{C}$) was imposed on mice for a time indicated in each experiment, as described previously.¹⁴ Briefly, mice were put into a cylindrical cage (36 cm diameter, 36 cm width), the wall of which was made of stainless steel rods (2 mm diameter, 1 cm apart). The cage was turned around a horizontal axis by an electric motor, the speed being indicated in each experiment. For the first 1–2 h of the experiment, most mice followed the rotation of the cage by walking on the steel rods using their fore- and hind-feet or by hanging from the rods rather than by walking. However, some mice spent this period revolving to higher positions then jumping to lower position. After this period, some mice became unable to follow the speed, as evidenced by alternate periods of walking and sliding, and later there was falling from the hanging position, with the number of mice falling becoming greater as walking was prolonged. In endurance experiments, whenever we observed falling or signs of distress (e.g., unsuccessful attempts to walk at the required speed), the mouse was immediately removed from the cage by a blinded investigator. In such experiments, the number of mice still walking was recorded at various time-points.

Assay of HDC Activity For the assay of HDC activity, mice were sacrificed by decapitation without anesthesia after the indicated duration of PW. Then, their quadriceps femoris muscles and brains were removed and stored at -80°C until assay. HDC activity was assayed using our previously published method²⁶ with a slight modification.^{14,27} Briefly, each tissue sample (less than 250 mg) was put into a cooled Teflon tube together with phosphorylated cellulose (50–100 mg) and 2.5 mL of ice-cold 0.02 M phosphate buffer (pH 6.2) containing pyridoxal 5'-phosphate (20 μM) and dithiothreitol (200 μM). This mixture was then homogenized using an Ultra Turrax homogenizer (Janke and Kunkel Co., Berlin, Germany). The supernatant obtained after centrifugation of the homogenate (10000 g for 15 min at 4°C) was used as the enzyme solution. The histamine in the tissues was bound to the phosphorylated cellulose and was removed almost completely from the enzyme solution by the centrifugation. Reaction mixture (1 mL) containing the enzyme solution was incubated at 37°C for 16 h with histidine (1 mM). After the enzyme reaction had been terminated by adding 2 mL of 0.5 M HClO_4 , the histamine formed during the incubation was separated by chromatography on a small phosphorylated cellulose column, then quantified fluo-

rometrically.²⁶ HDC activity was expressed as n mol of histamine formed during a 1 h period of incubation by the enzyme contained in 1 g (wet weight) of each tissue (nmol/h/g).

Quantitative Real-Time Polymerase Chain Reaction (PCR) Analysis of HDC mRNA Using Trizol reagent (Invitrogen, CA, U.S.A.), total RNA was extracted from the quadriceps femoris muscles of mice were sacrificed by decapitation without anesthesia at the time-points indicated in the relevant experiment. cDNA was prepared with the aid of a SuperScript first-strand synthesis system (Invitrogen) and subjected to quantitative real-time PCR analysis using iQ SYBR green (Bio-Rad, Hercules, CA, U.S.A.). Gene-specific primers were designed using DNASTar software (DNASTAR, Inc., Madison, WI, U.S.A.). The primers for 'HDC' expression were 5'-CCG AGG GGG AGG TGT CTT AC-3' (forward) and 5'-CGA GCC GAG CGT TCA GG-3' (reverse) and for 'endothelial nitric oxide synthase (eNOS)' were 5'-GGG CGG GGA GCG ACT ACT-3' (forward) and 5'-GCA GCA GCT TTG GCA TCT TCT-3' (reverse). The internal control primers for 'EF1a1' were F5'-ATT CCG GCA AGT CCA CCA CAA-3' and R5'-CAT CTC AGC AGC CTC CTT CTC AAA C-3'. The PCR profile was 3 min at 95°C for initial melting; 20 s at 95°C , 30 s at 58°C for 45 cycles; 30 s at 95°C for 1 cycle; and then 1 min at 55°C followed by stepwise temperature increases from 55 to 95°C to generate the melt curve. Standard curves and PCR efficiencies were determined for each primer set using control cDNA and a 10-fold dilution series ranging from 1000 to 1 ng/mL. Relative expression levels of 'HDC' were calculated as a function of 'EF1a1' expression.²⁸

Measurement of NO Metabolites Since NO is rapidly converted to the stable metabolites NO_2^- and/or NO_3^- (largely to the latter), the production of NO can be evaluated by measuring these metabolites.²⁹ Mice were sacrificed by decapitation without anesthesia and quadriceps femoris muscles were quickly removed and immediately homogenized in 2 vol of methanol. The homogenate was centrifuged at 10000 g for 10 min at 4°C . The supernatant was used for the analysis of NO metabolites (NO_2^- and NO_3^-). They were separated by a high performance liquid chromatography (HPLC), which includes systems converting NO_3^- to NO_2^- , converting NO_2^- to a chromophoric azo product by the Griese reaction,²⁹ and measuring its absorbance at 540 nm (ENO-20, EICOM, Japan). The results of the analyses are expressed as nmol/g tissue.

Measurement of Muscle Glycogen Muscle glycogen was measured by a conventional method,³⁰ using an enzymatic glucose-determining kit (Glucose-CII-test-Wako; Wako Pure Chemical Industries, Osaka, Japan).

Data Analysis Data from endurance tests were analyzed by Kaplan–Meier analysis using the log-rank test (GraphPad Prism, GraphPad Software Inc., San Diego, CA, U.S.A.). Experimental values are given as means $\pm$ standard deviation (S.D.). The statistical significance of the difference between two means was evaluated using a Student's unpaired *t* test. For analyzing multiple mean values, Tukey–Kramer or Fisher's protected least significant difference (PLSD) *post hoc* test was employed after analysis of variance (ANOVA) using the Statview-J 5.0 computer program (SAS Institute, Inc., U.S.A.). In these tests, *p* values less than 0.05 were considered to indicate significance.

Fig. 1. Induction of HDC in Quadriceps Femoris Muscles of C57BL/6 Mice Performing PW at a Speed of 9m/min

(A) Induction of HDC mRNA. Muscles were taken 2h after the start of PW and analyzed for HDC mRNA. Each value represents the mean±S.D. from 6 mice. * $p < 0.05$ vs. time 0. (B) Time course of the induction of HDC activity. Muscles were taken at the time-points indicated. Although 3h after the start of PW, some mice became unable to follow the required speed (repeatedly walking, then sliding), their muscles were used for measurement. The mice capable of following the speed were left in the cylindrical cage for the remainder of the periods of PW. Each value represents the mean±S.D. from 4 mice. * $p < 0.05$ and ** $p < 0.01$ vs. time 0.

Fig. 2. Effects of the H1-Receptor Antagonists Pyrilamine (A) and Fexofenadine (B) on PW-Endurance of C57BL/6 Mice

PW was carried out at a speed of 9m/min. Mice were given (A) saline or pyrilamine, or (B) vehicle or fexofenadine at the indicated dose at 1h after the start of PW, and PW-endurance monitoring was continued for the next 4h. $n = 8-17$ for each group. * $p < 0.05$ or ** $p < 0.01$ vs. mice injected with saline or vehicle.

RESULTS

Induction of HDC by PW in C57BL/6 Mice On the basis of preliminary experiments, PW was imposed on mice at a speed of 9m/min, except where otherwise noted. PW elevated both HDC mRNA and HDC activity in the quadriceps femoris muscle in C57BL/6 mice (Fig. 1). The HDC activity was greater at longer durations of PW. On the other hand, HDC activities in the brain were not different between time 0 (0.59 ± 0.05 nmol/h/g, $n = 5$) and time 5h after the start of PW (0.62 ± 0.05 nmol/h/g, $n = 5$). Thus, in the following experiments, we focused on the HDC in the quadriceps femoris muscles alone.

Effects of Histamine H1-Receptor Antagonists on PW-Endurance Pyrilamine and fexofenadine are histamine H1-receptor antagonists, and it is known that while the former acts on both peripheral and central receptors, the latter acts predominantly on peripheral receptors.³¹⁾ As shown in Figs. 2A and B, each of these antagonists (injected 1h after the start of PW) dose-relatedly reduced the PW-endurance abilities of C57BL/6 mice. In other words, these drugs appeared to promote fatigue during PW.

Effects of Histamine H2-, H3-, and H4-Receptor Antagonists on PW-Endurance Ranitidine, thioperamide, and JNJ-777120 are antagonists of histamine H2-, H3-, and H4-receptors, respectively. Ranitidine (injected 1h after the start of PW) tended (non-significantly) to reduce PW-endurance in C57BL/6 mice (Fig. 3A). When the data from C57BL/6 were statistically analyzed at 2h (but not at other time-points) after the start of PW, the differences between the saline group and the two groups given ranitidine were significant. However, C57BL/6 mice did not exhibit any significant changes in PW-endurance in response to thioperamide (injected 1h after the start of PW) (Fig. 3B). JNJ-777120 had no significant effects, either, in C57BL/6 mice under any conditions tested (various doses and injection timings) (data not shown).

Effects of an Irreversible HDC Inhibitor on PW-Endurance α -Monofluoromethylhistidine (FMH) is an irreversible (or suicide) HDC inhibitor.²²⁾ FMH strongly inhibits HDC in various tissues in mice at or around the dose used in the present study.^{32,33)} As shown in Fig. 4, FMH potentially promoted exercise-induced fatigue in C57BL/6 mice.

PW-Endurance and HDC Induction in HDC-KO and H1-KO Mice In the experiments described above, PW

Fig. 3. Effects of Ranitidine (A) and Thioperamide (B) on PW-Endurance of C57BL/6 Mice Performing PW at a Speed of 9 m/min

Mice were given (A) saline or ranitidine or (B) saline or thioperamide at the indicated dose at 1 h after the start of PW, and PW-endurance monitoring was continued for the next 4 h. $n=8-11$ for each group.

Fig. 4. Effects of FMH, an Irreversible HDC Inhibitor, on PW-Endurance of C57BL/6 Mice Performing PW at a Speed of 9 m/min

Saline or FMH (25 mg/kg) was given at 1 h after the start of PW, and PW-endurance monitoring was continued for the next 4 h. $n=13$ for each group. $**p<0.01$ vs. mice injected with saline.

was imposed on the mice at a speed 9 m/min. However, in preliminary experiments we noted that neither HDC-KO nor H1-KO mice could follow this speed. We therefore compared PW-endurance abilities between these KO mice and their control wild-type (WT) mice (C57BL/6) using a speed of 7.5 m/min. As shown in Figs. 5A and B, these KO mice displayed markedly less PW-endurance than the WT mice. Interestingly, HDC activity in the quadriceps femoris muscles of H1-KO mice, but not in those of the WT mice, was significantly elevated as early as 90 min after the start of PW (Fig. 5C).

Effects of Fexofenadine on Muscle NO Production and Glycogen Content As described in Introduction, the microcirculation is important in exercise, and histamine is a regulator of the microcirculation. Histamine-induced arteriolar vasodilation is largely mediated by histamine H1-receptors and the subsequent production of NO.³⁻⁵⁾ In addition, muscle

glycogen is an important energy source for exercise. Thus, we examined the effects of fexofenadine on the PW-induced production of NO and levels of glycogen in quadriceps femoris muscles.

Effects on NO Production As shown in Figs. 6A and B, fexofenadine did not affect the resting levels of NO metabolites. Unexpectedly, these resting levels were similar to those measured after 3 h PW (possibly, their rates of release from and production by the muscle were similar to each other).

However, after 3 h PW their levels were significantly lower in the fexofenadine group (this result was unexpected because eNOS is said to be a constitutive enzyme). These results suggest not only that PW activated eNOS, but also that it induced this enzyme to some extent *via* stimulation of peripheral histamine H1-receptors.

Effects on Glycogen Levels After 3 h PW, the level of muscle glycogen tended to be decreased, and it was significantly lower (*vs.* vehicle) in the fexofenadine group (Fig. 6D). This lower level in fexofenadine-treated mice may be causally related to their reduced PW-endurance (Fig. 2).

DISCUSSION

The results obtained from WT C57BL/6 mice, HDC-KO, and H1-KO mice may be summarized as follows. (i) PW increased HDC mRNA and HDC activity in quadriceps femoris muscles. (ii) Mice given one of two types of histamine H1-receptor antagonist (peripherally acting or both peripherally and centrally acting) or an irreversible HDC inhibitor exhibited less endurance than control mice. (iii) Mice deficient in HDC or histamine H1-receptors also exhibited less PW-endurance than control mice. (iv) The increase in HDC activity induced by PW was greater in the muscles of H1-deficient mice than in those of their WT controls. (v) Mice given the peripheral H1 antagonist fexofenadine displayed significantly reduced muscle levels of NO metabolites and glycogen after 3 h walking (*vs.* vehicle-treated mice), although this drug did not affect their resting levels. We discuss these findings in the following

Fig. 5. PW-Endurance of HDC-KO and H1-KO Mice, and HDC Induction in such Mice

(A,B) PW, at a speed of 7.5 m/min, was monitored for up to 5 h. $n=10-11$ for each group. $**p<0.01$ vs. the relevant WT control. (C) HDC induction in the quadriceps femoris muscle at 90 min after the start of PW in H1-KO and their WT control mice. Each value represents the mean $\pm$ S.D. from 8–11 mice. $**p<0.01$ vs. time 0 min.

Fig. 6. Effects of Fexofenadine on eNOS, NO_2^- , NO_3^- , and Glycogen Levels in Quadriceps Femoris Muscles in C57BL/6 Mice

In the resting group, muscles were taken 2 h after an injection of vehicle or fexofenadine (40 mg/kg) without PW. In the walking group, vehicle or fexofenadine was given at 1 h after the start of PW (9 m/min), and muscles were taken after an additional 2 h PW. Although some mice in this group became unable to follow the required speed (repeatedly walking, then sliding), their muscles were used for measurement. $n=6$ or 7 for each group. $*p<0.05$ between the indicated two groups.

paragraphs.

When discussing the present data, we need to consider whether the observed effects on endurance abilities could

reflect effects on the skeletal muscles themselves or on other organs (central nervous system, lung, heart, liver, etc.). PW induces HDC not only in skeletal muscles (quadriceps femo-

ris, pectoralis superficial, and masseter muscles),¹²⁾ but also in other organs and tissues (such as lung, spleen, and bone marrow),¹⁴⁾ indicating that PW may produce various effects on the whole body *via* the induction of HDC. However, in the present experiments, we observed no significant HDC elevation in brain after various time-points of PW in C57BL/6 mice (data not shown). In the present study, the peripheral H1 antagonist, fexofenadine, significantly reduced both PW-endurance and the muscle levels of NO metabolites and glycogen seen after 3 h walking. Thus, it may be the 'peripheral' effects of histamine (including effects in skeletal muscles) that are largely involved in favouring endurance and protecting against exhaustion.

Our present findings suggest that histamine is involved in protecting against exercise-induced fatigue or exhaustion. We previously reported that training decreases the magnitude of exercise-stimulated HDC induction,¹⁴⁾ and that starvation (which may promote fatigue) augments HDC induction in mice performing PW.¹⁴⁾ In the present study, the PW-endurance of H1-KO mice was less than that of WT C57BL/6 mice (Fig. 5B), while after PW the muscle HDC induction was larger in H1-KO mice than in WT mice (Fig. 5C). It is supposed that hypoxia might be an important factor to induce muscle fatigue. Indeed, a recent report has demonstrated that hypoxia-inducible factor-1 (HIF) has an HDC-inducing activity,³⁴⁾ suggesting that the less PW-endurance of H1-KO mice might be due to a larger production of HIF due to hypoxia. Collectively, the results obtained by the present study may also support the idea that (i) histamine or HDC induction may be important to reduce exercise-induced fatigue as a protective mechanism, and (ii) mice with a lower PW-endurance may need more HDC induction against hypoxia due to PW.

We speculate upon the mechanism underlying the protective effect of histamine as follows. It is known that histamine dilates arterioles and enhances capillary permeability *via* stimulation of H1 receptors and the ensuing production of NO, and these effects may help to promote the supply of nutrients and O₂ and the removal of waste products, including CO₂. In addition, Li *et al.* have reported that the induction of eNOS by histamine in human vascular endothelial cells is mediated by stimulation of H1-receptors.³⁵⁾ We previously showed that in mice PW also induces HDC in other peripheral organs with highly developed microcirculations (lung, spleen, and bone marrow).¹⁴⁾ Thus, HDC induction not only in skeletal muscles, but also in other peripheral organs, may help to prevent exercise-induced fatigue and/or aid the recovery from fatigue. Indeed, exercise-induced muscle NO production was significantly inhibited by fexofenadine, a peripheral H1 antagonist (Fig. 6). Therefore, HDC induction in skeletal muscles in response to exercise may be one of the defense mechanism that protects against exercise-induced fatigue or exhaustion. These ideas may be supported in part by the finding made in humans by Lockwood *et al.*¹⁶⁾ that H1 receptor-mediated vasodilation contributes to post-exercise hypotension and muscle hyperemia.

In conclusion, although the detailed mechanisms remain to be clarified, the results presented here support the ideas that in mice: (i) histamine is involved in protecting against exercise-induced fatigue or exhaustion, (ii) histamine exerts its protective effect *via* H1 receptors and the ensuing production of NO in skeletal muscle, and (iii) histamine is provided,

at least in part, by HDC induction in skeletal muscles during prolonged exercise.

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