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ORIGINAL PAPER

Ameliorative effect of tranexamic acid on physiological skin aging and its sex difference in mice

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Abstract

An effective method to protect the skin from natural aging is unknown. Therefore, in this study, we examined the ameliorative effects of tranexamic acid on natural skin aging. In addition, we examined the sex difference in the effect exhibited by tranexamic acid. We bred hairless mice without ultraviolet ray irradiation and physical stress for 2 years. During the study period, mice were orally administered tranexamic acid (12 mg/kg/day) three times per week. Development of signs of skin aging was found to be ameliorated by tranexamic acid. Furthermore, synthetic inhibition of plasmin was observed following tranexamic acid treatment. The synthetic reinforcement of hyaluronic acid by an increase in the number of epidermal cells and the degradative inhibition of extracellular matrix (ECM) by matrix metalloproteinase (MMP) suppression were observed. These results indicate that natural skin aging was ameliorated by tranexamic acid via the regulation of the plasmin/TGF-β/epidermal cells/hyaluronic acid and plasmin/MMPs/ECM signal transmission pathways. Taken together, sex difference was observed for the ameliorative effect of tranexamic acid on skin aging, with a stronger effect observed in females than in males. More importantly, we found that the synthesis of hyaluronic acid was stronger in female mice than in male mice.

Keywords Tranexamic acid · Natural aging · Plasmin · Transforming growth factor-β · Extracellular matrix · Hyaluronic acid

Abbreviations

MMP	Metalloproteinase
ECM	Extracellular matrix
uPA	Urokinase-type plasminogen activator
HAS2	Hyaluronan synthase 2
HAS3	Hyaluronan synthase 3

Introduction

Aging induces various alterations to each organ in humans. As skin alteration is irreversible, it serves as the best standard for evaluating aging. Skin aging is closely associated with environmental agents; photo-aging by ultraviolet rays (UV) is an especially important factor [25]. To prevent photo-aging, we must prevent UV contact with skin [13]. However, a clear protection method against physiological natural aging remains unknown.

Generally, wrinkles [15], slack [17], skin dryness [29], hair removal [27], gray hair [27], and senile skin disease [22] are observed by skin alteration that accompanies natural aging. Wrinkles and slack occur due to a decrease in connective tissue (extracellular matrix, ECM). For example, collagen I, the collagen fiber of the dermis, decreases. In addition, the volume of the filament is disproportioned and becomes thin [6]. During alteration of the ECM, functional deviations of fibroblasts [9], saccharification, and oxidative denaturation by retardation of protein turnover [7], and cross-linkage formation [8] are concerning.

In dryness of the skin, natural moisturizing factor (NMF) and intercellular lipid play important roles [23]. When these factors are reduced by aging, skin dryness occurs. Protein turnover also affects skin dryness [30]. Epidermal cells are converted to a horny cell, and this horny cell becomes dirt, which then separates from the skin [20]. This conversion cycle that occurs in elderly

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people is long; therefore, when a horny cell accumulates in excess, the stratum corneum becomes thick, and moisture can no longer spread, resulting in drying. In addition, the thickening of this stratum corneum causes skin dullness.

Recently, inflammation has become a concerning issue, as it is involved in the induction of skin aging. It has been reported that premature aging occurs when exposed to chronic acids via progressive, slight inflammation [14]. Owing to this reaction, DNA is damaged by reactive oxygen species, and telomere progression shortens, resulting in the promotion of accumulated aging cells. If aging of cell progresses, chronic inflammation will deteriorate, thereby inhibiting tissue reformation and accelerating the aging process. Reports have indicated that aging will accelerate if inflammation occurs even if neither a gene nor an environmental factor exists [14].

Previously, we reported that tranexamic acid, an anti-inflammatory agent, exhibited an effective function against photo-aging of the skin [11]. Therefore, we focused on skin aging and herein, aimed to investigate the effects of tranexamic acid on natural skin aging. Furthermore, we have reported that the effect of tranexamic acid on the skin displayed differences based on sex [10]. Therefore, we also examined the effect exerted by tranexamic acid on the natural aging of the skin based on sex.

Materials and methods

Animal experiments

Specific-pathogen-free (SPF) 8-week-old male and female hairless mice (SLC, Hamamatsu, Shizuoka, Japan) were used in this experiment. Mice were maintained in individual cages in an air-conditioned room at 23 ± 1 °C under SPF conditions with a 12-h light/dark cycle. In addition, the light source used was a fluorescent light with ultraviolet ray cuts (FLR110H.EX-D/M/36 WAN; Everise Inc., Maebashi, Gunma, Japan). There were ten mice per treatment group. These groups were: male control, male solvent administration, male tranexamic acid administration, female control, female solvent administration, and female tranexamic acid administration. Skin and blood samples were collected 2 years after the start of the experiment. The experiment also confirmed reproducibility by three independent assessments. This study was performed in strict accordance with the recommendations of the guide for the care and use of laboratory animals of Suzuka University of Medical Science (approval number: 34). All surgeries were performed under pentobarbital anesthesia and all efforts made to minimize suffering.

Tranexamic acid treatment

Approximately, 12 mg/kg of tranexamic acid (Daiichi Sankyo Healthcare Co., Ltd., Tokyo, Japan) in distilled water was orally administered to mice three times per week for 2 years, whereas solvent-administered animals were administered distilled water [5]; toxicity was not observed with long-term tranexamic acid administration.

Evaluation of the wrinkles

In accordance with the method of Bissett et al. [4], we scored the wrinkles of hairless mice 2 years after tranexamic acid treatment using the following chart: 0, no wrinkles; 1, light wrinkles; 2, slightly deep wrinkles; and 3, deep wrinkles.

Measurement of the capacitance of the dorsal skin

The capacitance of the stratum corneum (reflecting skin hydration in the outermost layer of the skin) was measured using a corneometer CM825 probe (Courage + Khazaka electronic GmbH) as described previously [3]. We measured the permeability in accordance with the procedure of Yokoyama et al. [31].

Preparation and staining of the dorsal skin

We obtained dorsal skin samples 2 years after the start of the experiment. Dorsal skin specimens were fixed in phosphate-buffered paraformaldehyde (4%), embedded in frozen Tissue Tek, an OCT compound, and cut into 5 µm sections. The sections were stained with hematoxylin–eosin (HE) in accordance with the established procedures to enable histological analysis of the skin. To assess collagen expression, samples were stained by the Masson trichrome technique [trichrome stain kit (modified Masson's); ScyTek Laboratories, Inc., Logan, UT, USA] [2].

Western blot analysis of the dorsal skin

We obtained the dorsal skin samples from mice 2 years after the start of the experiment. The skin samples were homogenized in lysis buffer (Kurabo, Osaka, Japan) and centrifuged at 8000×*g* for 10 min. Western blot analysis was performed as previously described [30]. The membranes were incubated at room temperature for 1 h with primary antibodies against plasmin (1:1000; Abgent, San Diego, CA, USA), urokinase-type plasminogen activator (uPA, 1:500; Abcam, Cambridge, MA, USA), hyaluronan synthase (HAS)2 (1:1000; Aviva, San Diego, CA, USA), HAS3 (1:1000; Bioss Antibodies Inc., Woburn, MA, USA), A100A4 fibroblast

marker (1:1000; Thermo Fisher Scientific, Fremont, CA, USA), collagen type I (1:1000; Millipore, Billerica, MA, USA), Laminin (1:1000; Abcam), fibronectin (1:1000; Abcam), or β-actin (1:5000; Sigma-Aldrich Corp., Saint Louis, MO, USA). The immune complex on the membranes was visualized with horseradish peroxidase-conjugated secondary antibody (Novex, Frederick, MD, USA) and detected with ImmunoStar Zeta regent (Wako, Osaka, Japan). The images of the membranes were acquired using the multi-grade software program (Fuji-film, Greenwood, SC, USA).

Quantification of matrix metalloproteinase (MMP)-1, MMP-2, MMP-3, hyaluronic acid and transforming growth factor TGF-β using an enzyme-linked immunosorbent assay

We extracted blood samples from the hearts of the test mice 2 years after the start of the experiments. The plasma levels of MMP-1, MMP-2, MMP-3, hyaluronic acid, and TGF-β were determined using commercial enzyme-linked immunosorbent assay (ELISA) kits (MMP-1: MyBioSource, San Diego, CA, USA; MMP-2: Sigma-Aldrich Corp.; MMP-3: R&D Systems, Minneapolis, MN, USA; hyaluronic acid: R&D Systems; TGF-β: R&D Systems) according to the respective manufacturer instructions.

Statistical analyses

All data are presented as mean ± standard deviation (SD). Results were statistically analyzed using Microsoft Excel 2010 with one-way analysis of variance (ANOVA) followed by Tukey's post hoc test using SPSS, version 20 (IBM, Aemonk, NY, USA). Differences were considered statistically significant at $p < 0.05$.

Results

Effect of tranexamic acid treatment on natural aging in the dorsal skin of aging mice

Moisture retention was observed to decrease in aging mice. However, when treated with tranexamic acid, moisture retention was ameliorated (Fig. 1a). Furthermore, the degree of this amelioration was greater in female than in male mice (Fig. 1a). Thickness of the dorsal skin in aging mice increased; however, this was suppressed by tranexamic acid treatment (Fig. 1b, c). Moreover, although mice had wrinkles due to aging, treatment with tranexamic acid ameliorated these wrinkles. This effect was markedly observed in female aging mice unlike in male mice (Fig. 1d, e).

Effect of tranexamic acid treatment on the expression of plasmin and uPA in aging mice

We examined plasmin, a target substance of tranexamic acid, and found that the expression of plasmin and uPA decreased in the aging mice when treated with tranexamic acid compared to that in the other groups; a difference based on sex was not observed for the expression of plasmin and uPA (Fig. 2).

Effect of tranexamic acid treatment on the plasma levels of MMP-1, MMP-2, and MMP-3 in aging mice

The plasma concentrations of MMP-1, MMP-2, and MMP-3 decreased in aging mice following tranexamic acid treatment; a difference based on sex was not observed with these enzymes (Fig. 3).

Effect of tranexamic acid treatment on the expression of total collagen, collagen I, fibronectin, and laminin in aging mice

We performed a histological examination of collagen expression on the skin. Tranexamic acid increased collagen expression in male and female mice (Fig. 4a). Furthermore, we examined the ECM, the target for MMP decomposition. The expression of collagen I, fibronectin, and laminin increased with tranexamic acid treatment. In addition, a difference based on sex was not observed in collagen I, fibronectin, or laminin level (Fig. 4b).

Effect of tranexamic acid treatment on the level of TGF-β in aging mice

The plasma level of TGF-β decreased in aging mice following tranexamic acid treatment; a difference based on sex was not observed in aging mice treated with tranexamic acid (Fig. 5).

Effect of tranexamic acid treatment on the expression of fibroblast, HAS2, HAS3, and keratin 10 in aging mice

As tranexamic acid has been indicated to affect TGF-β, we examined the expression of fibroblasts, HAS2, HAS3, and keratin 10 (marker of keratinocytes), which are influenced by TGF-β. Based on the expressions of fibroblasts (Fig. 6a) and HAS2 (Fig. 6b) in the dorsal skin, an alteration was not observed following treatment with tranexamic acid in both male and female aging mice. However, the expression of keratin 10 (Fig. 6c) and HAS3 (Fig. 6d) in the tranexamic acid

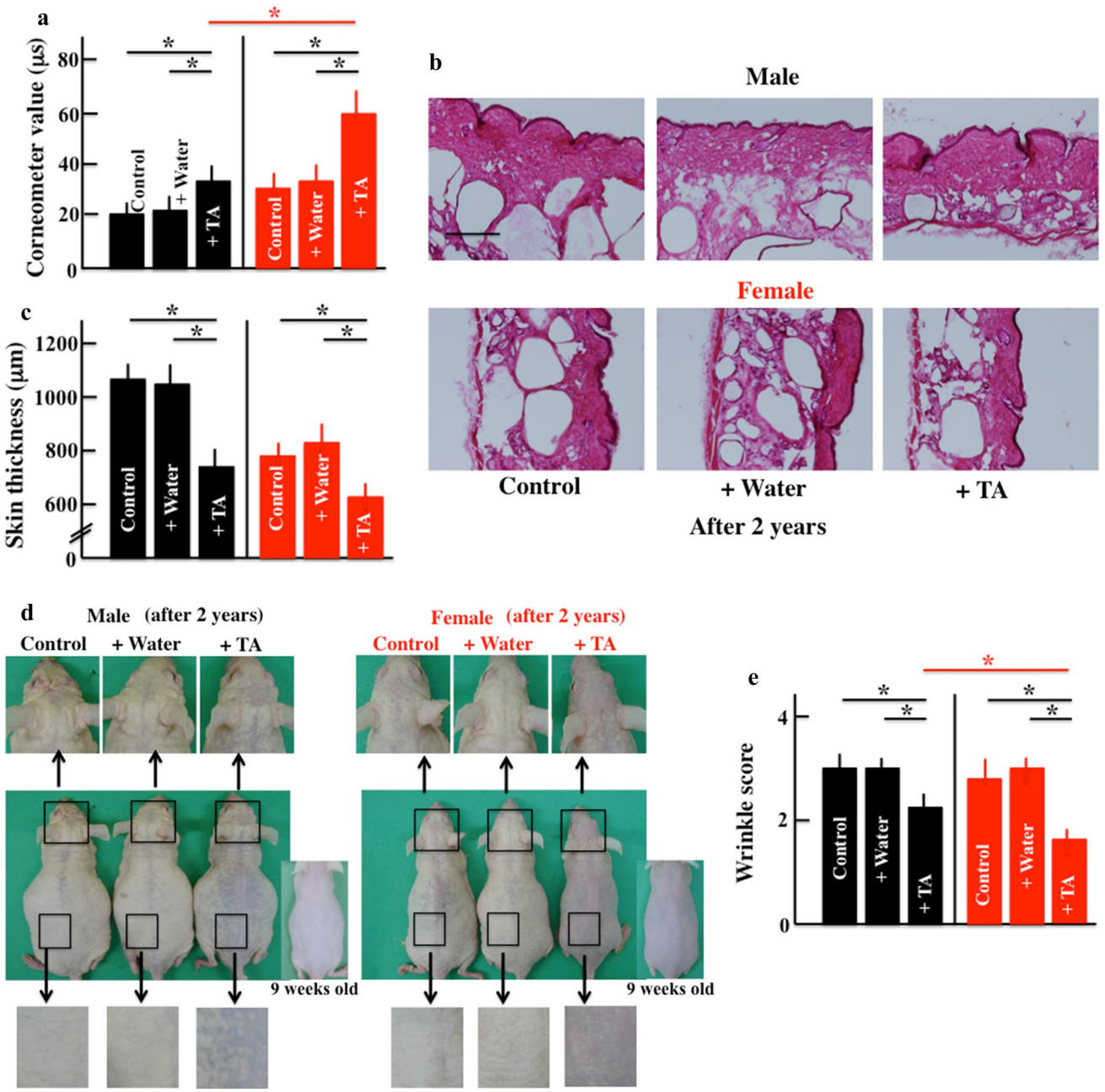

Fig. 1 Effects of tranexamic acid treatment on natural aging of the dorsal skin. 2 years after the start of the experiment, we measured corneometer value (**a**), skin thickness (**b**, **c**), and wrinkle score (**d**, **e**) in the dorsal skin of male and female hairless mice. TA: tranexamic acid. The values are expressed as mean ± standard deviation (SD) derived from six animals. *$p < 0.05$. Scale bar = 100 μm

treatment group was higher than that in the other groups. In addition, it exhibited greater marked effects in female than in male mice.

Effect of tranexamic acid treatment on hyaluronic acid in the dorsal skin of aging mice

Hyaluronic acid level in the dorsal skin of aging mice increased following treatment with tranexamic acid. When male and female mice were compared, the amount of hyaluronic acid by tranexamic acid treatment greatly increased in the female mice compared to that in male mice (Fig. 7).

Effect of tranexamic acid treatment on the plasma level of 17β-estradiol in aging mice

We measured the plasma level of 17β-estradiol to examine the cause of sex difference upon treatment with tranexamic acid.

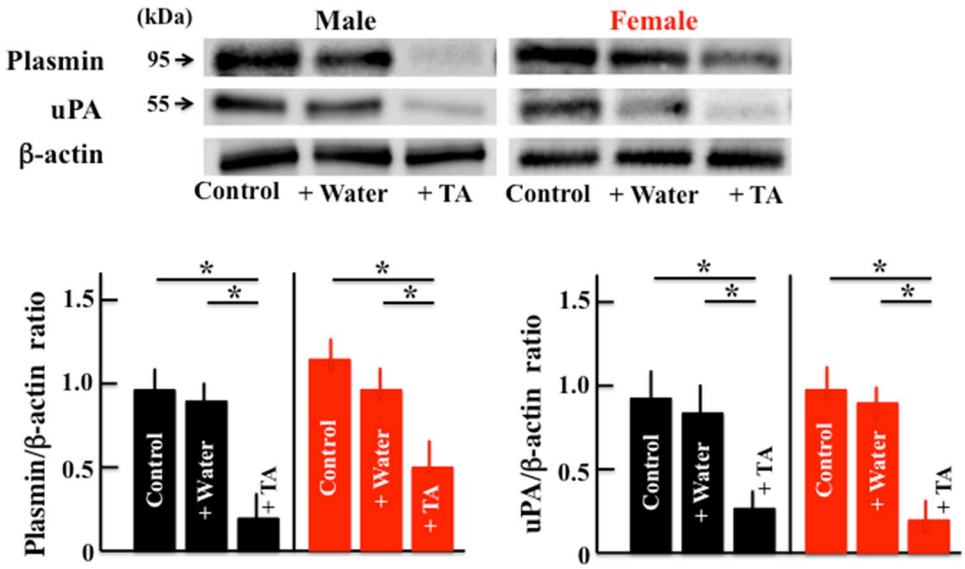

Fig. 2 Effects of tranexamic acid on the expression of plasmin and urokinase-type plasminogen activator. 2 years after the start of the experiment, we measured the plasmin and urokinase-type plasminogen activator in the dorsal skin of male and female mice by Western blot analysis. TA: tranexamic acid; uPA: urokinase-type plasminogen activator. The values are expressed as mean ± SD derived from six animals. *$p < 0.05$

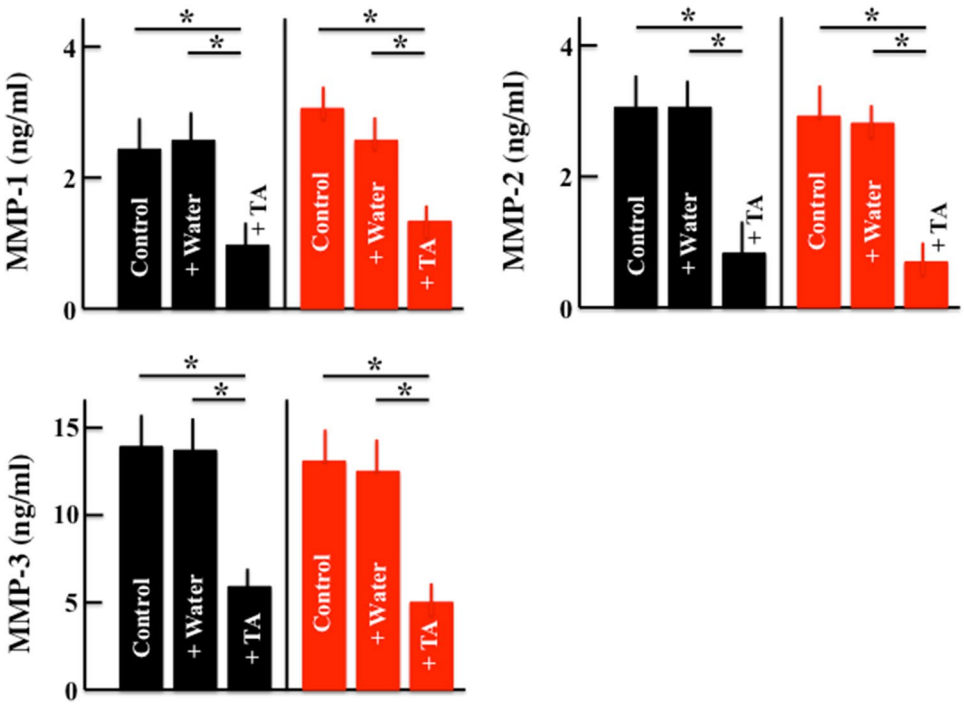

Fig. 3 Effects of tranexamic acid on the plasma levels of matrix metalloproteinase (MMP)-1, MMP-2, and MMP-3. 2 years after the start of the experiment, we measured the concentration of MMP-1, MMP-2, and MMP-3 in the plasma of male and female mice using an ELISA kit. TA: tranexamic acid; MMP: matrix metalloproteinase. The values are expressed as mean ± SD derived from six animals. *$p < 0.05$

In the aging male mice, 17β-estradiol level did not change with tranexamic acid administration. On the other hand, the level of 17β-estradiol in the tranexamic acid treatment group greatly increased in female mice compared to that in the other groups (Fig. 8).

Discussion

In this study, when tranexamic acid was used to treat mice for 2 years, moisture retention and thickening of the skin

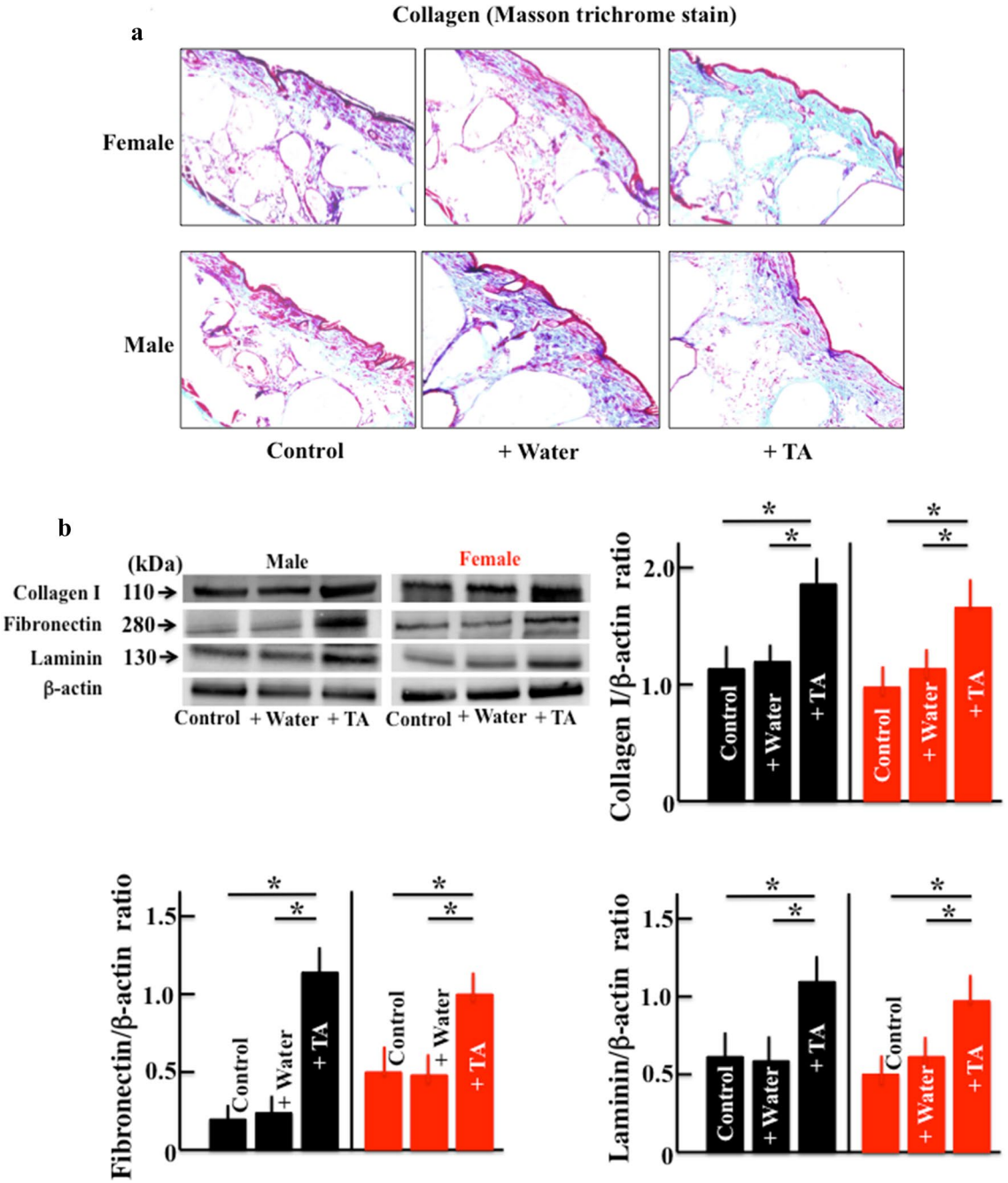

Fig. 4 Effects of tranexamic acid on the expression of histochemical collagen and extracellular matrix (ECM). 2 years after the start of the experiment, we stained collagen (**a**) and measured the ECM contents (collagen type I, fibronectin, and laminin) (**b**) in the dorsal skin of male and female mice. TA: tranexamic acid; ECM: extracellular matrix. The values are expressed as mean ± SD derived from six animals. *$p < 0.05$

were ameliorated. Furthermore, this ameliorative effect demonstrated by tranexamic acid was remarkable in female mice but not in male mice. In addition, the level of plasmin and uPA in the skin decreased by tranexamic acid administration when compared to that of the control. The expression of MMP and the degrading enzyme of ECM were inhibited; ECM is also connected to natural aging of the skin. The volume of the hyaluronic acid in connection with natural aging protection increased by tranexamic acid administration. This increase was higher in female mice than in male mice.

The main medicinal action of tranexamic acid is plasmin inhibition [1], and plasmin is known to promote the activation of MMP [16]. The cause of wrinkles, a sign of skin

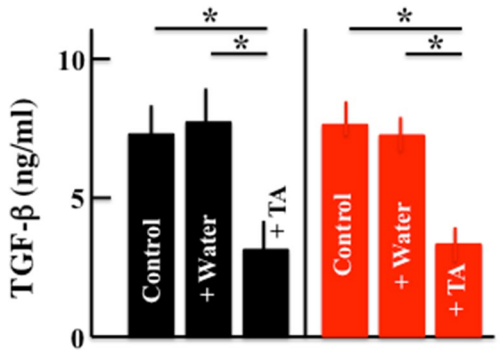

Fig. 5 Effects of tranexamic acid on the plasma level of TGF-β. 2 years after the start of the experiment, we measured TGF-β in the plasma of male and female mice using an ELISA kit. TA: tranexamic acid. The values are expressed as mean ± SD derived from six animals. *$p < 0.05$

aging, is based on a decrease in the ECM [21]. MMP-1, MMP-2, and MMP-3 decompose collagen I, fibronectin, and laminin, respectively, in the ECM. In this study, because the synthesis of plasmin was inhibited by tranexamic acid, the activity of MMPs was suppressed. As a result, skin aging was thought to be ameliorated via the suppression of ECM degradation.

Plasmin is also known to promote activation of TGF-β [19]. TGF-β is closely related to the metabolism of hyaluronic acid. Hyaluronic acids are the macromolecules contained in many saccharides of *N*-acetylglucosamine and D-glucuronic acid when combined [12]. Hyaluronic acid has high moisture retention ability and once decreased, a subsequent decrease in the moisture amount contained in the skin or a decline in cell metabolism occurs. Skin plasticity is then lost which promotes aging through wrinkle formation [18]. In fibroblast of the dermis, TGF-β stimulates the expression of HAS2 mRNA and promotes the synthesis of hyaluronic acid [26]. In the epidermal cells, TGF-β inhibits the expression of HAS3 mRNA and reduces the synthesis

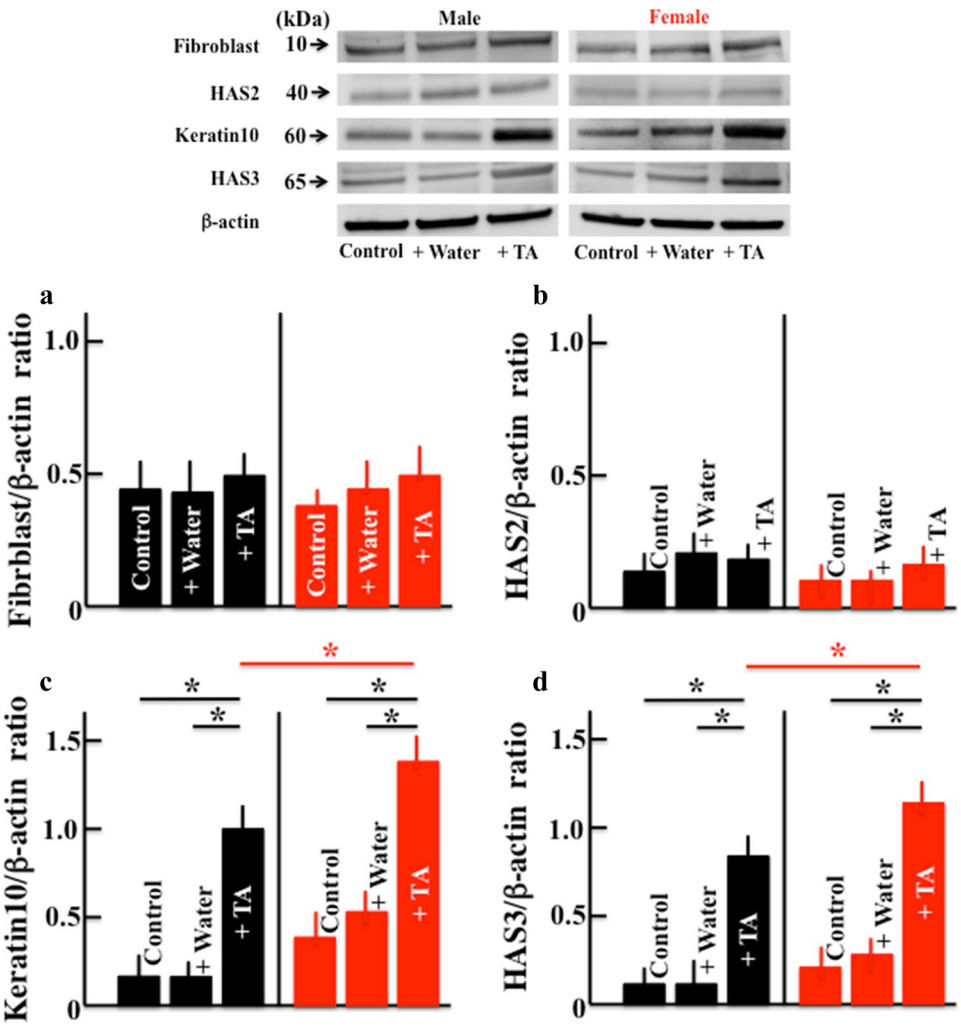

Fig. 6 Effects of tranexamic acid on the expression of hyaluronan synthases (HAS), fibroblast, and keratin 10 (marker of keratinocyte). 2 years after the start of the experiment, we measured the fibroblast, HAS2 (secreted from fibroblast), keratin 10, and HAS3 (secreted from keratinocyte) in the dorsal skin of male and female mice. TA: tranexamic acid. The values are expressed as mean ± SD derived from six animals. *$p < 0.05$

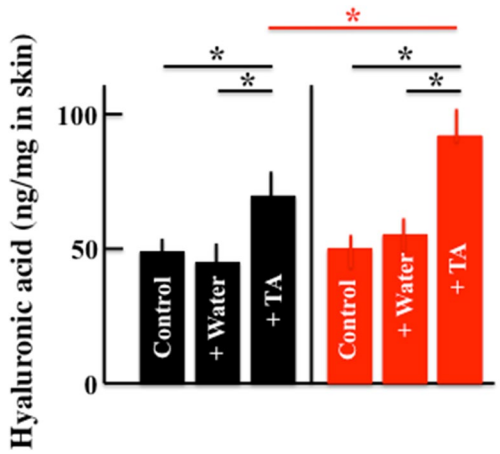

Fig. 7 Effects of tranexamic acid on the expression of hyaluronic acid. 2 years after the start of the experiment, we measured the concentration of hyaluronic acid in the dorsal skin of male and female mice using an ELISA kit. TA: tranexamic acid. The values are expressed as mean ± SD derived from six animals. *$p < 0.05$

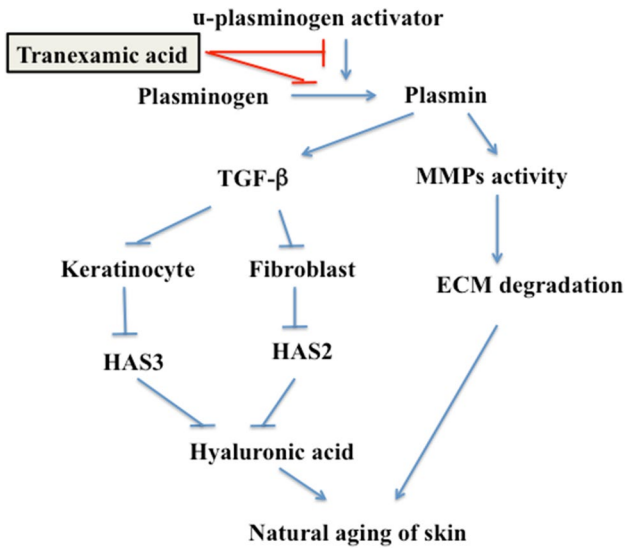

Fig. 8 Mechanism of the effect of tranexamic acid on natural skin aging in mice

of hyaluronic acid [24]. In this study, the activity of TGF-β declined by tranexamic acid administration. Based on the results obtained in the tranexamic acid-treated aging mice, it was seen that HAS2 expression level is inhibited in fibroblast and HAS3 is activated in epidermal cells. HAS3 and keratinocyte, a type of epidermal cell, were increased when tranexamic acid was administered. Therefore, based on the delayed effect on skin aging by tranexamic acid administration, the synthetic facilitatory effect of hyaluronic acid in epidermal cells may be concerning (Fig. 8). Following tranexamic acid administration, however, fibroblast and HAS2 did not differ from the control. Therefore, fibroblast decreases with aging on the natural status. Since fibroblast was greatly reduced, tranexamic acid was thought to exhibit few effects (data not shown). The relationship between tranexamic acid and fibroblast remains unclear, therefore, further examinations should be performed.

A difference based on sex was observed in the delayed effect exhibited by tranexamic acid on natural aging; the effect on females was higher than in males. A difference based on sex was not observed in the expression of ECM and MMP; however, for the expression of keratinocyte and HAS3, these levels were higher in female than male mice. Therefore, for the skin aging-delaying effect of tranexamic acid, the TGF-β/epidermal cells/HAS3/HA pathway is activated in female and not in male mice. This is because in the 2-year-old female mice, estradiol secretion was maintained, and the estradiol volume was greater with tranexamic acid administration than other groups (Fig. 9). Estrogen raises the proliferation of keratinocytes [28]. Therefore, it was thought that the female mice could suppress skin aging greater than the male mice. However, the mechanism by which tranexamic acid increases estrogen is not well known; therefore, future examinations are necessary.

Conclusion

Tranexamic acid exhibited a delayed effect on natural skin aging. By inhibiting the synthesis of plasmin and the plasminogen activator, tranexamic acid induced the synthetic increase in hyaluronic acid and inhibited ECM degradation. Therefore, amelioration of wrinkles on the skin and improvement in skin moisture were achieved. From the above results, skin aging in the elderly people can be delayed by consuming tranexamic acid. The anti-skin retrogradation

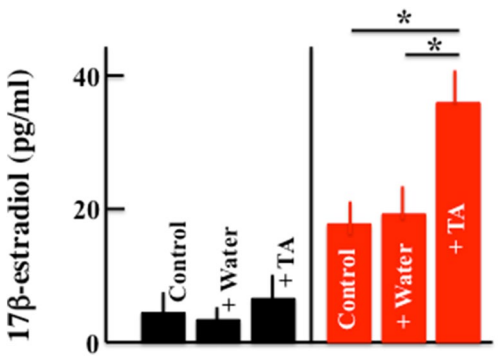

Fig. 9 Effects of tranexamic acid on the plasma level of 17β-estradiol. 2 years after the start of the experiment, we measured the concentration of 17β-estradiol in the plasma of male and female mice using an ELISA kit. TA: tranexamic acid. The values are expressed as mean ± SD derived from six animals. *$p < 0.05$

mechanism of tranexamic acid remains unknown; therefore, a clinical test on humans is also necessary and is currently being performed.

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Compliance with ethical standards

Conflicts of interest The authors declare no conflicts of interest in association with this study.

Ethical approval This study was carried out in strict accordance with the recommendations in the guide for the care and use of laboratory animals of Suzuka University of Medical Science (Approval number: 34). All surgery was performed under sodium pentobarbital anesthesia, and all efforts were made to minimize suffering.

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