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Original article

Sex differences regarding the amelioration of wrinkles due to skin dryness by the administration of tranexamic acid

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ABSTRACT

Tranexamic acid (trans-4-aminomethylcyclohexanecarboxylic acid) exerts an amelioration effect on wrinkle formation due to skin dryness. We examined the sex differences in this effect. We administered tranexamic acid (750 mg/kg/day) orally for 20 consecutive days to male and female Naruto Research Institute Otsuka Atrichia (NOA) mice, which naturally develop skin dryness. In the treated female mice, the amelioration effect on the wrinkle score, deterioration of transepidermal water loss (TEWL), capacitance, and decrease in the expression of collagen type I was stronger than in the male treated mice. Furthermore, the level of β-endorphin in the plasma and the expression of β-endorphin, μ-opioid receptor, and macrophages in the dorsal skin increased after the administration of tranexamic acid, and this increase was higher in female mice than in males. In addition, the macrophage production was increased by the administration of tranexamic acid in the ovary but did not change after administration in the testes. A histological examination revealed that these macrophages produce the β-endorphin, clarifying the source of the elevated levels. The amelioration effect in the female treated mice was decreased by the administration of clophosome (a macrophage inhibitor) to a degree that did not markedly differ from the effect observed in the male treated mice. These results suggest that the amelioration effect on wrinkles is stronger in female NOA mice than in males and that β-endorphin produced by macrophages plays an important role in this sex difference.

1. Introduction

Sex differences are observed in a number of vital reactions throughout the animal kingdom. For example, with regard to the skin, women perspire less than men, and women have excellent adiathermancy and strong resistance to cold [1]. Women are also reportedly more tolerant than men to physical stress (oxidative stress [2,3], psychological stress [4], mental stress [5]). Sex differences are also observed in illnesses. For example, in pneumothorax [6] or gout [7], men tend to show symptoms more often than women, while systemic lupus erythematous [8] and sideropenia anemia [9] tend to affect women more often than men. Even with skin infections, seborrheic dermatitis tends to occur more often in men than in women [10], while women more often have a metal allergy than man [11].

We can also see sex differences in the effects of medicine. Although various factors affect the efficacy of a medicine or the occurrence of adverse drug reactions, drug metabolism is one of the main factors. In humans, women tend to have a greater capacity than men to metabolize drugs in the liver *via* CYP3A4, a member of the cytochrome p-450 family, which are drug metabolism enzymes. In contrast, men tend to have a greater capacity than woman to metabolize drugs *via* CYP1A2. These sex differences in ability to metabolize drugs are likely due to female hormones [12,13]. Furthermore, in rats, cytochrome p-450 has been implicated in the drug metabolism process in both sexes (males, CYP2C11; females, CYP2C12), causing sex differences. The expression of these different cytochromes p-450 is not controlled by a sex hormone but is modulated based on the secretion pattern of growth hormones [14–16].

However, wrinkles induced by dryness can damage people's health. When moisture is lost from the skin, a decline in the number of skin cells and sclerosis can occur. These events can impair the barrier function of the skin, exacerbating skin disorders and aging [17,18]. Generally, prophylactic efforts such as protection from ultraviolet rays and the use moisturizers can help prevent such impairment. However, the sex differences in the mechanism of wrinkles genesis are unknown, and at present, sex is not taken

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into account when advising about treatment and prophylaxis for wrinkles.

We previously reported the utility of tranexamic acid as an anti-inflammatory agent for ameliorating wrinkles due to dry skin [19] and pigmentation following exposure to ultraviolet B radiation [20]. While we noted sex differences in the pigmentation amelioration effect [21], we did not examine the sex differences in the agent's effect on wrinkles.

We examined the sex differences in the wrinkle formation due to skin dryness of mice and investigated the mechanism behind these differences.

2. Materials and methods

2.1. Animal experiments

Specific-pathogen-free (SPF) 4-week-old male and female Naruto Research Institute Otsuka Atrichia (NOA) mice (CLEA, Suita, Osaka, Japan) were used in the experiments. The NOA mice are model mice which exhibit natural skin dryness [22,23]. The mice were kept individually in cages in an air-conditioned room at 23 ± 1 °C under SPF conditions. There were 10 mice per group. Skin, ovary, testes, and blood samples were collected 20 days after the start of the experiment. This study was carried out 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 were made to minimize suffering.

2.2. Tranexamic acid treatment

Approximately 750 mg/kg of tranexamic acid (Daiichi Sankyo Healthcare Co., Ltd., Tokyo, Japan) in saline was administered orally for 20 consecutive days, while saline was administered to the control animals [20].

2.3. Clodronate liposomes (neutralizing: clophosome) treatment

Approximately 0.2 ml of clodronate liposomes (macrophage inhibitor; FormuMax Scientific Inc., Palo Alto, CA, USA) in saline was injected intraperitoneally into the mice every other day during

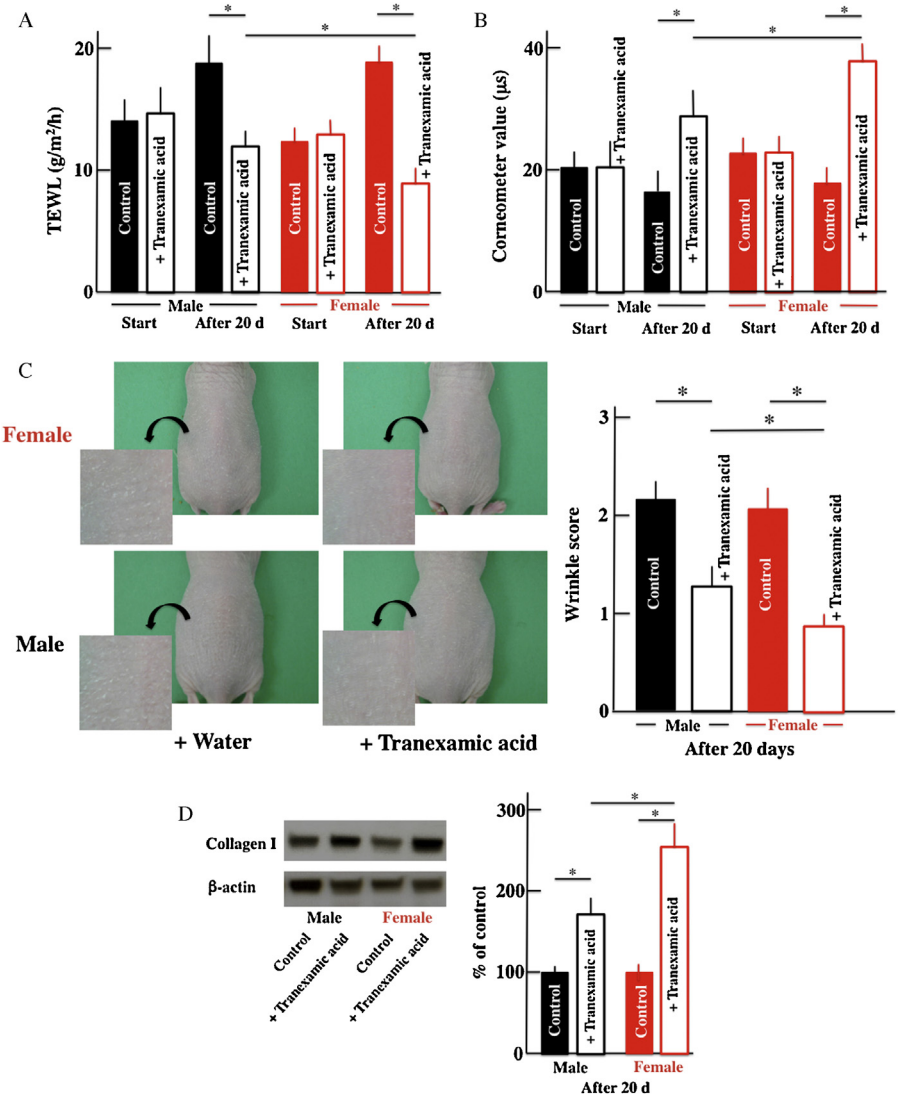

Fig. 1. The sex differences in the TEWL (A), moisture retention (B), wrinkle formation (C), and the expression of collagen type I (D) in the dorsal skin of tranexamic acid-treated NOA mice. Twenty days after the start of the experiment, we measured the TEWL, corneometer value, wrinkle score, and level of collagen type I in the dorsal skin of male and female NOA mice. Tranexamic acid (750 mg/kg) was administered orally for 20 consecutive days. The values are expressed as the mean ± SD derived from 10 anumals. *$p < 0.05$.