Dear Editor,

Cholinergic urticaria (CholU) is characterized by pinpoint-sized wheals with itching and/or stinging pain under sweating conditions, including hot bathing, physical exercise and emotional stress. The type I hypersensitivity to sweat is proposed to be involved in its pathogenesis. Indeed, more than 60% of patients with CholU shows immediate-type skin reactions upon intradermal injection of autologous sweat, and histamine release from basophils against the semi-purified sweat antigen in histamine release assay (HRA). Histamine released from skin mast cells also plays an important role in the development of wheals in CholU. In this study, we examined histamine concentrations in sweat of patients with CholU to describe a role of sweat histamine in the wheal formation of CholU.

Nine patients with CholU and 10 healthy volunteers (control) were recruited along with enrollment of seven patients with atopic dermatitis (AD) and seven patients with chronic spontaneous urticaria (CSU) (Supplementary Table 1). Following exercise for 15–30 min, a sauna at 50 °C for 10 min, a bath in hot water or emotional stress, sweat was collected by using a syringe from subjects’ skin of the head/neck or the trunk/extremities. The amount of histamine in sweat/plasma was measured by a high-performance liquid chromatography system. HRA in response to the semi-purified sweat antigen was performed by using the subjects’ basophils as described previously. This study was approved by the institutional review board of Hiroshima University Hospital (approval number, E-1420).

Median histamine concentrations in sweat of patients with CholU, AD or CSU, and healthy controls were 90.8, 30.8, 3.84 and 39.7 ng/ml without significant difference (Fig. 1a). They were much higher than histamine concentrations in plasma of healthy subjects (n = 5; mean ± SE, 0.89 ± 0.18 ng/ml). Thus, levels of sweat histamine concentration largely varied among individuals and were not related to specific diseases. However, significant higher histamine concentrations in sweat were detected in subjects with high histamine release (>5%) against the semi-purified sweat antigen in HRA (sweat allergy+) than those with low histamine release (sweat allergy-) (median, 86.8 vs 17.5 ng/ml; cut off value, 79.9 ng/ml) (Fig. 1b, Supplementary Fig. 1). There was also positive correlation between histamine release from the subjects’ basophils in response to the sweat antigen in HRA, and histamine concentrations in sweat (Fig. 1c).

To find bioactivity of histamine detected in sweat, we assessed concentrations of histamine to induce flare and wheal by the intradermal injection to healthy volunteers, and compared with histamine concentrations in sweat. Histamine concentrations at or higher than 100 ng/ml and 1000 ng/ml induced significant flare and wheal formations (Fig. 2a,b). In four patients with CholU, a patient with AD and three controls, sweat histamine concentrations were higher than the minimum concentration to induce flare upon intradermal injection (>100 ng/ml). In one patient with CholU and one control, they were high enough even for wheal induction (>1000 ng/ml).

In this study, we demonstrated that levels of histamine concentration in sweat obtained from patients with CholU were much higher than those in human plasma. Such high histamine concentrations in sweat were also detected in patients with AD or CSU and even in healthy controls. It was associated with type I hypersensitivity against the semi-purified sweat antigen rather than the presence of specific diseases such as CholU, AD and CSU. Moreover, histamine concentrations in the sweat of 8 subjects were higher than the minimum concentration of histamine to induce skin reactions upon intradermal injection. High concentrations of sweat histamine may be due to the penetration of histamine which released from skin mast cells in response to sweat antigen in the proximity of the sweat glands and ducts. Indeed, it is noteworthy that sweat histamine in all nine subjects with more than 15% histamine release in response to the sweat antigen was higher than 25 ng/ml (Fig. 1c). However, several subjects showed high histamine concentrations in their sweat with low basophil histamine release (<5%) activity in response to the sweat antigen, regardless of the presence of CholU, AD or CSU and even in healthy controls (Fig. 1b,c, Supplementary Fig. 2). Since histamine can be produced not only by skin mast cells but also by epidermal keratinocytes, histamine released from epidermal keratinocytes around the pore of sweat duct may also be stored or intermingled in sweat in a manner independent from sweat allergy. In addition, the specific development of flare and wheal reaction upon sweating by patients with CholU is a matter of discussion. It may be induced by a leakage of sweat with high concentration of histamine into the dermis through sweat ducts. No skin reaction should be developed even with high histamine in sweat as long as sweat is retained in the sweat gland apparatus as in healthy individuals. In fact, the leakage of sweat into the dermis due to the impaired tight junction has been reported in patients with AD and CholU.
Fig. 1. (a) Histamine concentrations in sweat of patients with CholU, AD or CSU and healthy controls. The median values of each group were 90.8, 30.8, 3.84 and 39.7 ng/ml without significant difference. (b) Histamine concentrations in sweat in the context of type I hypersensitivity to sweat (sweat allergy). The subjects whose basophils released high histamine (>5%) in response to the semi-purified sweat antigen in HRA (sweat allergy+) showed significantly higher concentrations of sweat histamine than the subjects with low histamine release in HRA (sweat allergy-) (p = 0.012). (c) The relationship of sweat histamine concentrations and histamine release in response to the semi-purified sweat antigen in HRA (using regression analysis; p < 0.05 was considered statistically significant). Histamine concentrations in sweat positively correlated with histamine release. CholU, cholinergic urticaria; AD, atopic dermatitis; CSU, chronic spontaneous urticaria; HRA, histamine release assay.

Fig. 2. Biological activity of histamine concentration detected in sweat in reference to the size of wheals and flares induced by intradermal injection of histamine at indicated concentrations. Intradermal injections of histamine at 100 ng/ml and 1000 ng/ml or higher, but not at 10 ng/ml and 100 ng/ml or less induced significant skin reactions of flare (a) and wheal (b), respectively.
Ilves et al. reported the presence of histamine in the sweat of patients with AD (8.67 ± 15.3 ng/ml) and healthy donors (13.0 ± 34.1 ng/ml) collected from the back of subjects after exercise. The reason for the discrepancy in histamine concentration between their report and ours remains unclear. The concentration of sweat histamine was not affected by the site of collecting sweat and the methods of perspiration, such as via heat or exercise provocation (Supplementary Fig. 3). Moreover, no decrease of histamine concentration was observed after incubation at 37 °C for 60 min in 8 sweat samples (Supplementary Fig. 4), implying the absence of substance decomposing histamine in sweat. Further study, exploring the possibility of the presence of substances neutralizing histamine activity in sweat and the mechanism to condensate sweat histamine on the skin surface or sweat gland may explain the large variation of histamine concentrations in sweat among subjects and the mechanism of wheal-and-flare formation in CholU. Collectively, we demonstrated much higher levels of histamine concentration in human sweat than those in plasma in association with sweat allergy. It may be involved in the pathomechanism of CholU cooperating with the leakage of sweat into the dermis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2019.08.011.

Conflict of interest

The authors have no conflict of interest to declare.

References


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