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REVIEW ARTICLE

Review Series: Advances in Consensus, Pathogenesis and Treatment of Urticaria and Angioedema

Pathogenesis of Cholinergic Urticaria in Relation to Sweating

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ABSTRACT

Cholinergic urticaria (CU) has clinically characteristic features, and has been frequently described in the literature. However, despite its comparatively old history, the pathogenesis and classification remains to be clarified. CU patients are occasionally complicated by anhidrosis and/or hypohidrosis. This reduced-sweat type should be included in the classification because the therapeutic approaches are different from the ordinary CU. It is also well-known that autologous sweat is involved in the occurrence of CU. More than half of CU patients may have sweat hypersensitivity. We attempt to classify CU and address the underlying mechanisms of CU based on the published data and our findings. The first step for classification of CU seems to discriminate the presence or absence of hypersensitivity to autologous sweat. The second step is proposed to determine whether the patients can sweat normally or not. With these data, the patients could be categorized into three subtypes: (1) CU with sweat hypersensitivity; (2) CU with acquired anhidrosis and/or hypohidrosis; (3) idiopathic CU. The pathogenesis of each subtype is also discussed in this review.

KEY WORDS

acetylcholine, acetylcholine receptor, anhidrosis, hypohidrosis, sweat hypersensitivity

INTRODUCTION

Cholinergic urticaria (CU) is a rare condition, but its incidence might be higher than that expected by general physicians. CU is clinically characterized by pinpoint-sized, highly pruritic wheals. Although the symptoms subside rapidly, commonly within one hour, CU may significantly impair the quality of life, especially sporting and sexual activities.[1] This unique disease was described by Duke in 1924,[2] however, despite its comparatively old history, the pathogenesis and classification remains to be clarified. CU is typically provoked by stimulation such as exercise, warmth, and emotional distress, which increases the body core temperature and promotes sweating.[3,4]

Since acetylcholine is known to induce both sweating and wheals when injected intradermally,[4] it has been considered that this sweating-associated, syringeal orifice-coincident wheal is mediated by acetylcholine. In fact, acetylcholine stimulation can elicit hives as seen in CU, suggesting that the etiology of CU includes certain events that are triggered by a cholinergic stimulus. A well-known hypothesis has been put forward to explain the pathogenesis of CU. The patients are hypersensitive to unknown substances in their sweats and develop wheals in response to sweat substance leaking from the syringeal ducts to the dermis possibly by obstruction of the ducts.[5,6] This "sweat hypersensitivity" hypothesis has been supported by the fact that not all but some patients with CU exhibit a positive reaction to intradermal injection of the patients' own diluted sweat as well as acetylcholine.[7] Based on the distinct responses to the autologous factors and clinical characteristics, Fukunaga *et al*. proposed two subtypes in the entity of CU, sweat hypersensitivity (non-follicular) type and follicular type.[7]

However, sweat hypersensitivity theory lacks suffi-

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cient evidence and can not encompass the whole etiology of CU. CU is occasionally associated with depressed sweating, as reported under the name of anhidrosis (complete lack of sweating) or hypohidrosis (incomplete lack of sweating).[8] There have been reported 29 patients with CU with anhidrosis and/or hypohidrosis in the literature,[8-32] and notably, 26 patients are Japanese. This type of CU may be caused by reduced expression of acetylcholine receptor but not by sweat hypersensitivity, as described below. In addition, two Japanese patients with CU had episodes of seizures upon occurrence of urticaria.[33,34] Given that acetylcholine mediates epileptic seizures,[35,36] seizures possibly occur when steroid therapy induces the re-expression of acetylcholine receptors in the brain.

By exploring the enigmatic relationship between wheal formation and sweating, we have addressed the general mechanism underlying CU.[37] In this review, we show the relationship between sweating and the pathogenesis of CU according to the published findings and propose the classification of CU based on the mechanisms.

CLINICAL SUBTYPES OF CU ACCORDING TO RESPONSES TO SWEAT

Since CU is not a homogeneous disease, its classification is necessary for the clinical use. However, few attempts have been performed to classify CU in the literature, and there is no solid consensus on the categorization. Horikawa *et al*. observed that a strong hypersensitivity to sweat was not observed in all CU patients and assumed other factors than sweat hypersensitivity are also involved in the pathogenesis of CU.[38] Some patients with chronic urticaria have autoantibodies to FcεRI or IgE, and the autologous serum skin test (ASST) has been used to detect the autoantibodies.[39,40] Horikawa *et al*. also found that 8 of 15 patients with CU showed responsiveness to ASST. While the follicular manifestation of wheal was mainly associated with positive ASST, the non-follicular hives tended to show strong hypersensitivity to sweat and were probably associated with sweat ducts. Based on this observation, they proposed to classify CU into two subtypes: (1) the sweat hypersensitivity type (non-follicular type) showing non-follicular hives, strong hypersensitivity to autologous sweat, development of satellite wheals following acetylcholine injection, and negative ASST; and (2) the follicular type showing follicular hives and positive ASST without hypersensitivity to autologous sweat or satellite wheals.[38] It remains unclear how ASST induces the follicular eruption. It is notable that some CU patients have hypersensitivity to both autologous sweat and serum.

In the above simple classification, it should be clarified whether the sweat and serum hypersensitivities can encompass the whole spectrum of CU. In addition, there are some important issues to be dissolved. CU patients are occasionally complicated by anhidrosis and/or hypohidrosis. This reduced-sweat type should be included in the classification because the therapeutic approaches are different from the ordinary CU. It has been thought that the anhidrosis and/or hypohidrosis are caused by obstruction of sweat orifice. However, the sweat reduction is not necessarily associated with poral obstruction. Nakamizo *et al*. proposed four subtypes of CU: (1) CU with poral occlusion; (2) CU with acquired generalized hypohidrosis; (3) CU with sweat allergy; and (4) idiopathic CU.[41] The incidence of overlapping of (1)-(3) is an important issue to elucidate their independence and concurrence.

One of the interesting observations in CU is that the sweat ducts are obstructed by lymphocytic inflammation around the ducts, and resultant retention and subsequent leakage of sweat from the damaged ducts induce wheals because of sweat hypersensitivity.[5,6] Given this mechanism, CU with anhidrosis and/or hypohidrosis might belong to all of "CU with poral occlusion", "CU with acquired generalized hypohidrosis", and "CU with sweat allergy". However, several observations concerning CU with anhidrosis and/or hypohidrosis are not in accordance with the conventional poral occlusion/sweat leakage theory. First, the symptoms are usually exacerbated in winter and resolved in summer, although it can be explained with the hypothesis that daily sweating in summer inhibits the formation of keratotic plugs to prevent the occurrence of CU.[6] However, the vast majority of this type of CU have been reported from Asia, whose climate is hot and humid, and the disease is rare in Europe, where it is cool and dry. This regional divergence in the occurrence of the disease is not consistent with the poral occlusion/sweat leakage theory. Second, in the literature, few of the patients with CU with anhidrosis or hypohidrosis showed positive results of the intradermally injected autologous sweat, suggesting that sweat hypersensitivity is not responsible for this form of CU. In addition, if sweat hypersensitivity is the mechanism, the anhidrotic area should be the predilection site for wheals, but wheals cannot occur on the anhidrotic area.[37] We found mosaic distribution of hypohidrotic or anhidrotic areas on the body surface, and the patients develop wheals on the hypohidrotic area. Therefore, we suggest that "CU with acquired generalized hypohidrosis" and "CU with poral occlusion" are mostly independent.

Considering all these findings, the first step for classification of CU seems to discriminate the presence or absence of hypersensitivity to autologous sweat. The second step is proposed to determine whether the patients can sweat normally or not. With these data, the patients could be categorized into three subtypes: (1) CU with sweat hypersensitivity; (2) CU with acquired anhidrosis and/or hypohidro-

Table 1 Clinical subtypes of CU according to responses to sweat

Subtype	Sweat allergy	Anhidrosis/ hypohidrosis	Intradermal test for acetylcholine	Pathology	Treatment
Sweat hypersensitivity	Positive	None	Positive	Infiltrate of lymphocytes around sweat glands	Desensitization
Anhidrosis or hypohidrosis	Mostly negative	Necessary, mosaic	Partial positive	Normal	Systemic steroid
Idiopathic	Negative	None	Negative	Normal	Antihistamines

sis; (3) idiopathic CU (Table 1). It is suggested that only a small percentage of the patients belong to the combination of (1) and (2).

ASSESSMENTS OF SWEAT HYPERSENSITIVITY

Several studies have suggested the involvement of autologous sweat in the occurrence of CU, as represented by the well-known finding that a considerable percentage of the patients show positive reactions to diluted own sweat by intradermal tests.[5,7,8,42] In this procedure, sweat is collected after exercise from the forearm of each patient, sterilized by using a 0.45-mm polyethersulfone membrane, and preserved at -80℃ until use. Sweat samples are diluted at 1 : 100 with physiological saline before the skin test. Serum is simultaneously obtained by centrifugation of venous blood. Samples of autologous diluted sweat (0.02 mL), autologous serum (0.05 mL), and 0.9% sterile saline as control (0.02 or 0.05 mL) are separately injected intradermally into the forearm of each patient at the time when they have no wheal. The diameters of wheals and erythema are measured 15 min after injection. Reactions are assessed as positive when the diameter of wheal induced by sweat and serum is 6 mm or more. The sterile saline, 0.05 and 0.02 mL, usually induces mild edema less than 4 mm and less than 2 mm, respectively. In our study, 11 (64.7%) of 16 patients with CU showed positive reactions to their own 1/100 diluted sweat by skin test.[7] Hide *et al*. have developed histamine release test (HRT) using leukocytes of patients,[42] which is more reliable than skin test. Results of skin test may be affected by both sweat constituents and skin conditions such as hypersensitivity, whereas HRT with standardized semi-purified sweat represents basophile conditions regardless of the constituent of sweat of individual subjects. This assay has been already commercialized. The collection of sweat is not an easy manipulation. HRT could be a potent practically beneficial tool to screen sweat hypersensitivity. Recently, they developed also histamine release-neutralization (HRN) assay by using the semi-purified and standardized sweat antigen, and showed high sensitivity (0.87) and specificity (0.522) to type I hypersensitivity against sweat in patients with AD and/or CU.[43]

ASSESSMENTS OF SWEATING CONDITION

CU is occasionally accompanied by anhidrosis or hypohidrosis. The sweating condition can be evaluated by exercise-induced sweating, which is assessed by iodine-starch test. Provocation is performed by exercise using an ergometer. The areas of hypohidrosis and anhidrosis are identified with iodine-starch staining.[6] In this assessment, normal hidrotic areas are changed from white to dark blue, whereas the anhidrotic skin remains white. To clarify the area of anhidrosis, photographs of both areas are taken, and skin biopsy specimens can be taken from both anhidrotic and hypohidrotic areas for further histological examination. In CU patients with anhidrosis or hypohidrosis, we have clearly demonstrated that the depressed-sweat areas are divided into the two areas, anhidrotic and hypohidrotic ones, and there is no normal sweating area in the patients.[37] Although sweating is reduced in the hypohidrotic area, a substantial degree of sweating is still observed, as compared to the anhidrotic area, where complete lack of sweating is seen. As judged from the four patients, anhidrotic areas are seen in a large mosaic pattern, and the four limbs and face may be the predilection sites.[37]

ROLE OF ACETYLCHOLINE IN CU

Acetylcholine is known to induce degranulation in rat mast cells.[44,45] Subcutaneous injection of a cholinergic agent, carbaminoylcholine, induced sweating and numerous pin-point hives that are similar to CU.[42] Thus, it is believed that acetylcholine plays an essential role in the development of CU. On the other hand, there is a skeptical opinion for acetylcholine, as it remains unclear whether acetylcholine stimulates degranulation from human mast cells. To address the issue, we used LAD2 cells, a human mast cell line, for *in vitro* assay, and found that acetylcholine dose-dependently induced the degranulation of the mast cells,[37] suggesting an essential role of acetylcholine in the development of CU.

PATHOGENESIS OF CU WITH SWEAT HYPERSENSITIVITY

Tanaka *et al*. found that the sweat-induced release of histamine from basophils is mediated by specific IgE for the partially purified antigen present in the sweat of patients with atopic dermatitis.[46] The sweat hyper-

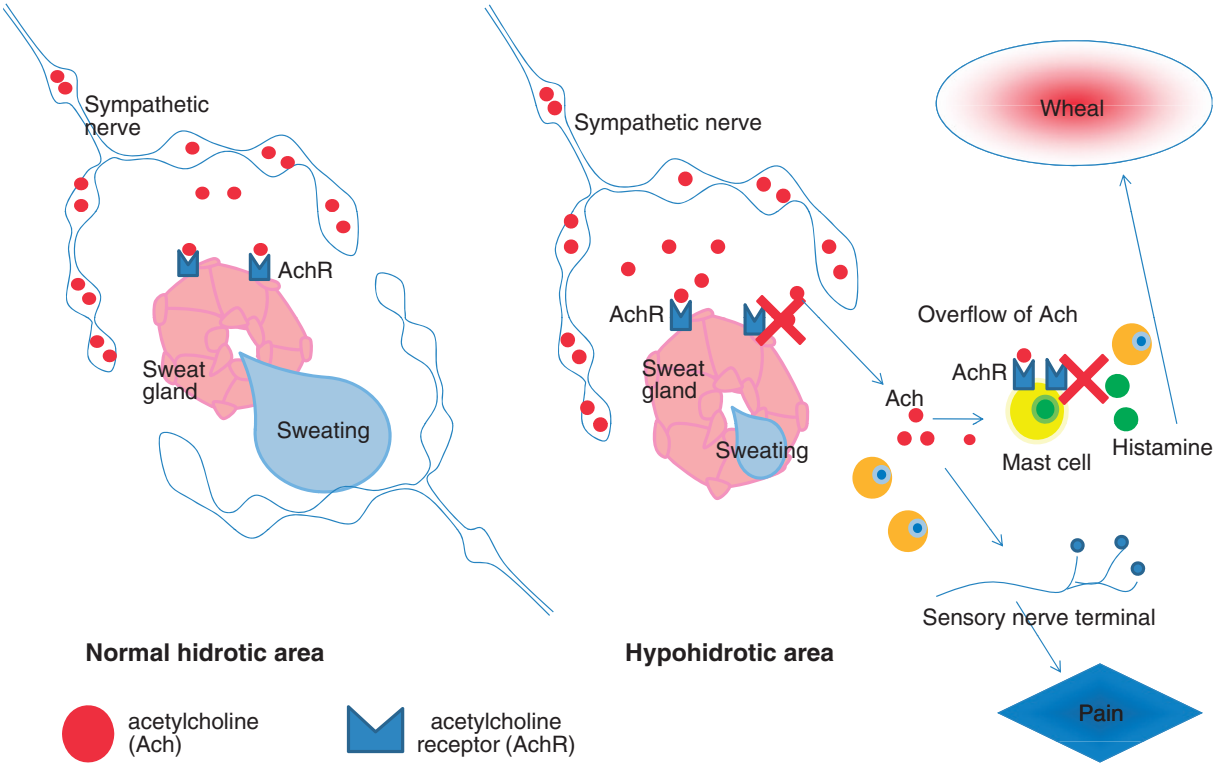

Fig. 1 A schematic model of the induction of wheals and pain in CU with hypohidrosis. In the normal hidrotic area, acetylcholine released from nerves upon exercise is completely trapped by acetylcholine receptor of eccrine glands and normally induces sweating. In the hypohidrotic area, acetylcholine released from nerves upon exercise cannot be completely trapped by acetylcholine receptor of eccrine glands and overflows to the adjacent mast cells. Subsequently, degranulation of the mast cells induces wheals and pain.

sensitivities of CU and atopic dermatitis seem to be virtually the same, and therefore, the sweat-induced histamine release from basophils may also be mediated by a specific IgE for sweat in atopic dermatitis as well as CU. The response depends on the concentration of sweat to some extent, which is compatible with the clinical observation that few patients with CU develop urticaria with small amount of sweating. Takahagi *et al*. recently reported that 23 (65.7%) of 35 CU patients associated with atopic diathesis showed basophil histamine release with semi-purified sweat antigen.[47] More than half of CU patients may have sweat hypersensitivity. Based on the observation that wheals are coincident with perspiration points of sweating, it is assumed that sweating causes pin-point wheals at sweat ducts that might allow sweat to leak.[38] However, there has been no strong evidence for the sweat leak to the dermis.

PATHOGENESIS OF CU WITH ANHIDROSIS AND/OR HYPOHIDROSIS

Various causes of anhidrosis or hypohidrosis have been reported, including absence of sweat glands, impaired function of sweat glands, poral occlusion,[6] or dysfunction of sympathetic nerves in neuropathies.[48] The causes are a matter of controversies. We address the mechanism based on our recent study.[37] As described in the clinical subtypes chapter, the sweat-depressed areas can be divided into two distinct areas; the hypohidrotic area, where a substantial degree of sweating is still observed, and the anhidrotic area, where the skin completely lacks sweating. By examining the sweating condition on the whole body surface, it was revealed that anhidrosis and hypohidrosis comorbid in the patients with CU.[37] Of note is the observation that the patients develop wheals in the hypohidrotic but not anhidrotic area, demonstrating that the occurrence of wheals is associated with sweating. In consistent with the result of the exercise induction test, wheals are provoked by the intradermal acetylcholine injection in the hypohidrotic but not anhidrotic area.

We performed the morphological and functional analyses of sweat glands in CU patients and found the involvement of acetylcholine receptor for sweating. In the anhidrotic and hypohidrotic areas, there is the gradient disturbance of the expression of cholinergic receptor muscarin 3 (CHRM3). CHRM3 is not expressed in the anhidrosis area, but its expression is retained to some extent in the hypohidrotic area. His-

tologically, there is an infiltrate of $CD4^+$ and $CD8^+$ T cells around the eccrine glands in the anhidrotic area, suggesting the inflammation-attenuated expression of the acetylcholine receptor. The expression pattern of CHRM3 on mast cells is similar to the eccrine gland epithelial cells in the anhidrotic and hypohidrotic areas. Acetylcholine receptor mediates wheal development,[48-50] and acetylcholine can induce degranulation of mast cells, as shown in our study,[37] and the past studies.[44,45] The data lead to the theory that CHRM3 expression is responsible for both sweating and wheal development. In the hypohidrotic area, we are tempting to speculate that acetylcholine released from nerves upon exercise cannot be completely trapped by acetylcholine receptor of eccrine glands and overflows to the adjacent mast cells (Fig. 1). In this scenario, it is assumed that mast cells can produce histamine in response to acetylcholine, because mast cells in the hypohidrotic area express some degree of CHRM3.[37]

IDIOPATHIC CU

CU is generally categorized into two major subtypes, CU associated with or without sweat hypersensitivity. We propose that the majority of CU patients with anhidrosis and/or hypohidrosis belong to CU associated without sweat hypersensitivity. However, there still exist unclassified patients with CU despite full examinations. Such patients without any clue to diagnosis are categorized into idiopathic CU. We need to further clarify the causative agents and underlying mechanism in this type of CU.

TREATMENT OF CU

Desensitization with autologous sweat has recently been attempted in CU with sweat hypersensitivity. Tanaka *et al*. demonstrated that desensitization using partially purified sweat antigen was effective in a patient with CU.[51] Kozaru *et al*. performed rapid desensitization with autologous sweat in 6 CU patients with sweat hypersensitivity, and succeeded in 5 of the 6 patients.[52] Desensitization therapy may become a familiar choice of treatment for CU patients with sweat hypersensitivity. A severe CU patient with sweat allergy has been successfully treated with an anti-IgE antibody, omalizumab,[53] suggesting that an IgE-mediated response is involved in the pathogenesis of CU. One of the first line treatments of CU with anhidrosis and/or hypohidrosis is the pulse therapy with a high dose of corticosteroid. The treatment may decrease the lymphocytic infiltrate around the sweat glands and allow acetylcholine receptor to re-express, resulting in the improvement of sweating and CU. Anti-histamines should be combined with other treatments owing to the limited effect. Various therapeutic variations including scopolamine,[54] danazol,[55,56] β2-adrenergic stimulants[57] and β2-adrenergic blockers[58] have been reported, however, those therapies are the second line treatments and recommended to be used as combination therapies.

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