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Review Article

Direct and indirect action modes of acetylcholine in cholinergic urticaria

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Abbreviations:

Ach	acetylcholine
AI GA	acquired idiopathic generalized anhidrosis
CHRM3	cholinergic receptor M3
CholU	cholinergic urticaria
CUAH	CholU with anhidrosis and/or hypohidrosis

ABSTRACT

Cholinergic urticaria (CholU) manifests small, itchy and/or painful wheals occurring upon perspiration and mechanically involving acetylcholine (Ach). Although a considerable number of studies have been conducted, the pathomechanisms underlying perspiration-associated release of histamine remain to be elucidated. We have proposed that CholU can be categorized into two major subtypes: Ach-indirectly induced, sweat allergic type and Ach-directly induced, depressed sweating type. In the former type, Ach evokes perspiration, and some sweat antigen(s) leaking from the sweat ducts to the dermis may stimulate mast cells to release histamine. In this scenario, the ducts might be damaged or obstructed for sweat leakage, and patients frequently exhibit positive autologous sweat skin test, representing "sweat allergy (hypersensitivity)". On the other hand, the latter Ach-mast cell directly interacting type, typically seen as "CholU with anhidrosis and/or hypohidrosis (CUAH)", eccrine sweat gland epithelial cells lack cholinergic receptor M3 expression. The expression of cholinergic receptors is completely absent in the anhidrotic areas and only slightly expressed in the hypohidrotic areas. In the hypohidrotic area, where pinpoint wheal occurs, it is hypothesized that released Ach cannot be completely trapped by cholinergic receptors of eccrine glands and overflows to the adjacent mast cells, leading to wheal formation. Thus, sweat allergy is not a requirement in this depressed sweating type. Although some additional complications, such as angioedema, anaphylaxis, and cold urticaria, have been documented, these two types represent the modes of action of Ach in this enigmatic urticaria.

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Introduction

Urticaria is a common skin disease, but it has many different subtypes in the clinical features, triggering causes, and pathogenetic factors. Cholinergic urticaria (CholU) is a characteristic type whose clinical feature is represented by discernible pinpoint-sized wheal (Fig. 1a). It mostly takes place on the syringeal orifice or may occur coincidentally with hair follicles. CholU is also characterized by painful sensation as well as itch. This clinically unique urticaria is typically provoked by perspiration-inducible stimuli, such as exercise, bathing, and sweating.^{1–3} Since acetylcholine (Ach) induces sweating and provokes wheals when injected intradermally, it has been thought that CholU is mediated by Ach.

The mechanisms of CholU remain unfully elucidated and are a matter of debate.^{3,4} Ach induces degranulation of mast cells,^{5,6} but this direct effect of Ach on histamine secretion has not been given a high priority in the mechanisms of CholU. One reason for this minimal estimation is that Ach release from sympathetic nerve induces sweating but not wheal in healthy individuals. Mast cells seem to be unexposed to Ach in a physiological condition. Some pathological mechanisms are required for operation of direct interaction between Ach and mast cells.⁷

Historically, the indirect Ach-mast cell interaction drew attention rather than the direct interaction, because the sweat allergy (hypersensitivity) theory was generally attracted. In the mechanism behind this theory, eccrine sweat ducts or orifice are obstructed in association with lymphocytic inflammation around the ducts, and resultant retention and subsequent leakage of sweat from the damaged ducts induce wheals.^{8,9} A drawback of this theory is that the direct contact of mast cells with Ach is negated and is not a requirement.^{3,4} Ach plays only a perspiration-promoting role, and allergy to dermally leaking sweat may evoke wheals. More recently, we found that the expression of Ach receptors on the eccrine epithelial cells is decreased in CholU

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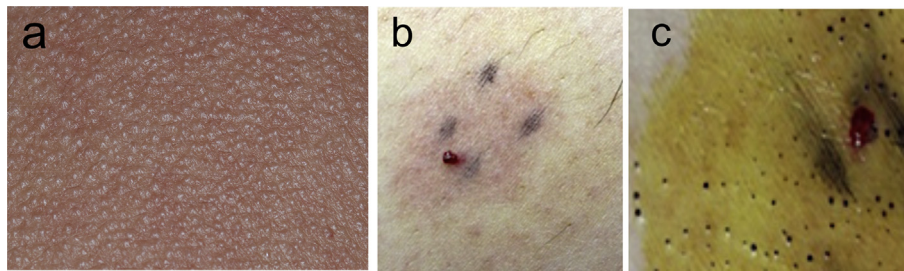


Fig. 1. Clinical appearance of CholU and Ach injection test. (a) Pinpoint wheal of CholU. (b) Satellite wheal around intradermal injection of Ach. (c) Sweating around Ach injection site as assessed by the iodine-starch technique.

accompanied by reduced perspiration.⁶ This gave rise to another theory in the pathogenesis of CholU.

In this review, we summarize current understanding of the mechanisms of CholU. In particular, we highlight the direct and indirect roles of Ach for mast cell stimulation.

Clinical tests for CholU

To better understand the mechanisms underlying CholU, I first mention the clinical tests for this complicated disease. Provocation of pinpoint wheal by exercise is a standard test for CholU, but wheal is not always inducible by this clinical mimicry because of ambiguity of the exercise standard or warmth method. To more certainly induce wheal and to classify the subtypes of CholU, intradermal injection tests with Ach, sweat, and serum are used as an alternative.^{4,10} The development of satellite wheals around the injection site is considered positive (Fig. 1b) and is seen in one-half to one-third of CholU patients. Simultaneously, sweating state around the injection site can be assessed by the iodine-starch technique (Fig. 1c). It has been thought that the positive result represents high sensitivity to Ach. However, it is unclear whether the Ach sensitivity reflects the susceptibility to CholU. In fact, the expression of cholinergic receptors is perturbed in a certain group of the patients with CholU, and the injection of Ach in those patients results in negative responses. Thus, we cannot predict the CholU susceptibility with Ach skin test.

A part of CholU patients show positive autologous sweat skin test,^{8–10} representing sweat allergy (sweat hypersensitivity).¹¹ However, there is no disease specificity, because patients with atopic dermatitis also show positive results at a high frequency.¹¹ *In vitro* tests, such as basophil histamine release and basophil activation-associated surface markers, are also used for evaluation of sweat allergy.^{11,12}

Ach-indirectly induced, sweat allergic type

Although the pathogenesis of CholU remains unclear, both direct and indirect theories in the interaction of Ach with mast cells have been put forward to explain the perspiration-associated histamine secretion from mast cells. Therefore, we have proposed the two major types of CholU: Ach-indirectly induced, sweat allergic type, and Ach-directly induced, depressed sweating type (Table 1).

In the former sweat allergic type, some antigen(s) leaking from the syringeal ducts stimulate dermal mast cells to release histamine (Fig. 2). In this scenario, Ach serves as only a stimulator for perspiration and does not directly contact mast cells. Upon sweating, the intradermal ducts might be obstructed or damaged for sweat leakage, and patients theoretically exhibit positive autologous sweat skin test.^{3,8,9} This hypothesis has been supported by high frequency of positive autologous sweat skin test as well as positive Ach skin test in the patients.¹³ In addition to this *in vivo* test, sweat allergy is also proven *in vitro* by basophil histamine release test and basophil activation test.^{11,12} In a Korean study, it was noted that positive autologous sweat skin test and basophil histamine release test were detected in only 37.5% of CholU patients.¹⁰ Meanwhile, it was reported that 65.7% of CholU patients associated with atopic diathesis showed basophil histamine release with semi-purified sweat antigen.¹⁴ Thus, when the CholU patients are accompanied by atopic condition, the frequencies of positive sweat tests seem to be elevated. Interestingly, it was found that claudin-3 expression is decreased in sweat glands of atopic dermatitis patients, resulting in sweat leakage.¹⁵ Therefore, the presence of sweat allergy depends on the concomitant atopic dermatitis.

Concerning sweat antigens, *Malassezia globosa*-derived substance, MGL_1304, was identified as a major allergen in human sweat for patients with atopic dermatitis¹⁶ and CholU.¹⁷ These patients have high levels of serum IgE to purified MGL_1304 from sweat,¹⁶ suggesting that the *Malassezia*-derived substance plays a causative role for the diseases.

Ach-directly induced, depressed sweating type (CUAH)

Mast cells are one of the crucial targets of Ach, as Ach is historically known to induce degranulation and subsequent histamine release in mast cells.^{5,6} We also confirmed that Ach can evoke significant degranulation in mast cell line LAD2.⁷ Since mast cells infiltrate in the vicinity of sympathetic nerves, these *in vitro* findings strongly suggest that Ach stimulate mast cells to secrete histamine in some pathogenic clinical settings (Fig. 2). Since wheal does not occur upon sweating in normal healthy individuals, it is considered that mast cells are unexposed to Ach in a healthy condition. It is an issue to clarify the pathological condition that allows mast cells to expose to Ach.

Table 1
Two subtypes of cholinergic urticaria.

Subtype	Involvement of Ach	Sweat allergy	Sweating	CHRM3 expression	Possible mechanism
Ach-indirectly induced, sweat allergic type	Indirect effect of Ach on mast cells	High frequency	Not impaired	Not impaired	Damage of sweat ducts
Ach-directly induced, depressed sweating type	Direct effect of Ach on mast cells	Low frequency	Low	Low	Overflow of Ach to mast cells

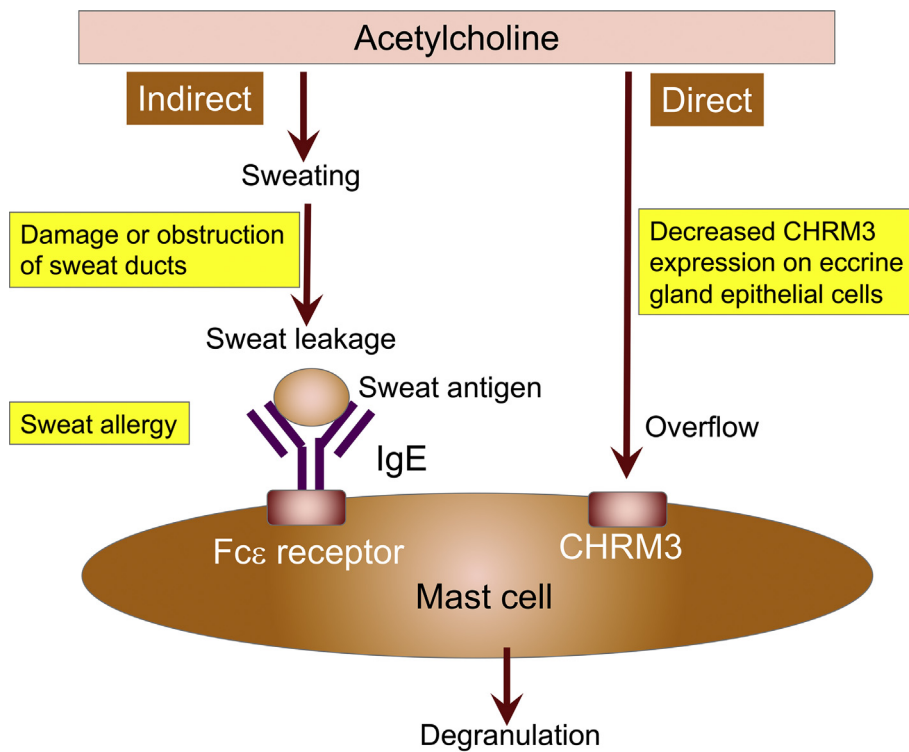


Fig. 2. Direct and indirect actions of acetylcholine in cholinergic urticaria. Left, Ach-indirectly induced, sweat allergic type. Right, Ach-directly induced, depressed sweating type.

There is a subpopulation of ChIU that is associated with depressed perspiration, encompassing anhidrosis (complete lack of sweating) to hypohidrosis (incomplete lack of sweating).¹⁸ This subtype of ChIU has been reported under the name of “ChIU with anhidrosis and/or hypohidrosis (CUAH)”. On the other hand, neurologists coined the term “acquired idiopathic generalized anhidrosis (AIGA)”, or more specifically, “idiopathic pure sudomotor failure (IPSF)”,¹⁹ which is often accompanied by ChIU. Thus, CUAH and AIGA are within the same disease spectrum, and the extent of ChIU is varying in the spectrum. Most of cases of CUAH have been

reported from Japan, and Western cases are scarce.⁷ This makes the world-wide classification of ChIU difficult.

In CUAH, the disordered perspiration is not homogenous over the skin. The skin surface of depressed sweating can be tentatively divided into the two areas, anhidrosis and hypohidrosis, as assessed by iodine-starch test.⁷ Typically, the predilection sites of anhidrosis include the four extremities, especially the distal parts, face, and back, while the chest and axillae are hypohidrotic areas (Fig. 3). Sweating is usually maintained in the palms and soles. When the patients are successfully treated with corticosteroid pulse therapy,

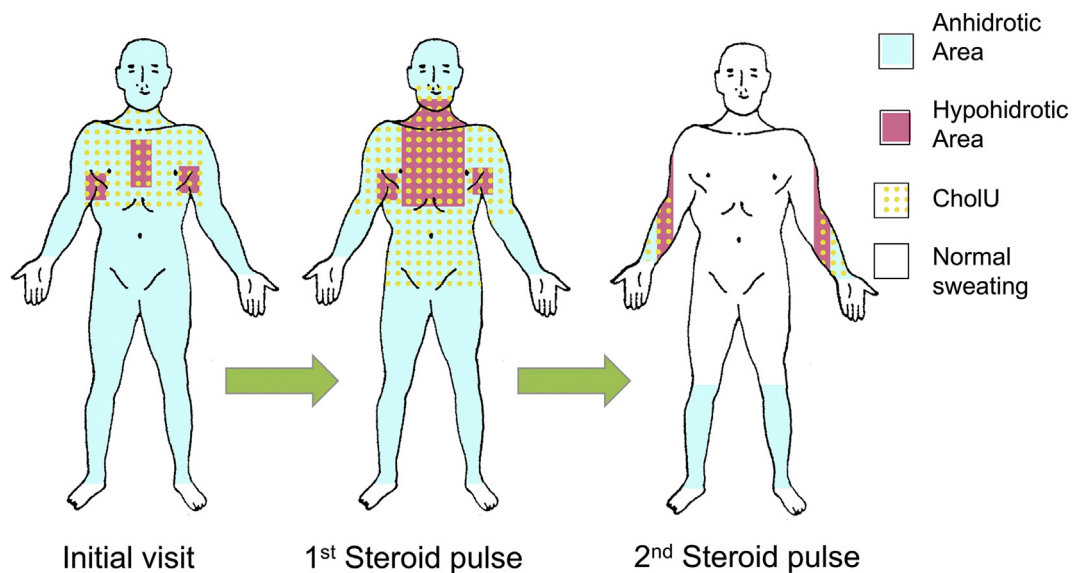


Fig. 3. Typical sweating condition and improvement before and after corticosteroid pulse therapy. Blue, anhidrotic area. Red, hypohidrotic area. Yellow dots, wheal occurring area.

the anhidrotic area is gradually diminished and replaced by the hypohidrotic area, which is then further improved to normal sweating area.²⁰ Thus, the extension of the hypohidrotic area to the anhidrotic area is the first noticeable change. A careful observation reveals that wheals occur on the hypohidrotic areas, but not on the anhidrotic areas. Therefore, CholU tends to take place on the recovering area.²⁰ Whereas Ach injection induces no reaction at the anhidrotic site, it can produce wheal at the hypohidrotic area.

The cholinergic receptor mediates CholU.^{21–23} By a binding assay, it was demonstrated that muscarinic Ach receptors are reduced in the skin of patients with CholU.²² Accordingly, we found that CUAH patients lack cholinergic receptor M3 (CHRM3) expressed on the eccrine sweat gland epithelial cells (Fig. 4).⁷ Compared to non-anhidrotic/hypohidrotic CholU, CHRM3 expression is decreased in CUAH (Fig. 4, upper panel). The expression of CHRM3 is completely absent in the anhidrotic areas, while it is incompletely decreased in the hypohidrotic areas (Fig. 4, lower panel). It should be noted that lymphocytes infiltrate in the anhidrotic skin, indicating the association of CHRM3 decrease with the inflammatory infiltration. Along with CHRM3 expression, the expression of Ach esterase, a processing enzyme of Ach, is also decreased in CUAH.^{25,26}

Mast cells are present just in the vicinity of eccrine glands and share the pattern of CHRM3 expression with the eccrine epithelial cells.⁷ In the anhidrotic area, neither eccrine gland epithelial cells nor mast cells express CHRM3, indicating that sweating and wheal formation are absent in this area. In the hypohidrotic area, we are tempting to speculate that Ach released from nerves is not completely trapped by cholinergic receptors of eccrine glands and overflows to the adjacent mast cells, leading to wheal formation (Fig. 5). In this scenario, mast cells can produce histamine in response to Ach via CHRM3 whose expression is low but still functional in the hypohidrotic area. The injection of autologous sweat or serum do not produce positive reactions in either

hypohidrotic or anhidrotic area. These findings are in accordance with the fact that sweat allergy is virtually absent in CUAH.^{7,27}

Lymphocytic infiltration around eccrine sweat glands in ach-directly induced, depressed sweating type (CUAH)

It is histopathologically known that lymphocytes infiltrate around eccrine glands in some patients with CholU. Historically, different lines of studies have suggested that two pathogenic consequences may follow the lymphocytic infiltration. The first consequence is the damage or obstruction of sweat ducts and the resultant dermal leakage of sweat. In the second one, the CHRM3 expression on sweat gland epithelial cells is decreased by the infiltrating lymphocytes. The first and second outcomes are related to the Ach-indirectly induced, sweat allergic type, and the Ach-directly induced, depressed sweating type (CUAH), respectively. It appears that each of these two consequences occurs almost exclusively. We consider that the second one is more closely associated with lymphocytic infiltration.²⁶ As shown earlier in Figure 4, lymphocytes infiltrate around eccrine glands in the sweating-depressed, lesional skin of CUAH patients.⁷ The infiltrate consists of both CD4⁺ and CD8⁺ T cells, and as assessed by the expression of CXCR3 and CCR4, both Th1/Tc1 and Th2/Tc2 subpopulations are identifiable.²⁶

In CUAH, it is unlikely that the inflammatory change induces the damage of sweat ducts and resultant sweat allergy, because CUAH patients show no autologous sweat skin test.⁷ Instead, the T cell infiltration seems to attenuate CHRM3 expression, as the number of lymphocytes infiltrating in eccrine glands inversely correlates with the expression levels of CHRM3.²⁴ The non-trapped Ach by eccrine epithelial CHRM3 may overflow to adjacent mast cells, leading to histamine release (Fig. 5).

CholU is frequently associated with atopic dermatitis,^{26,28} implying that Th2-skewing condition might be dominant in not

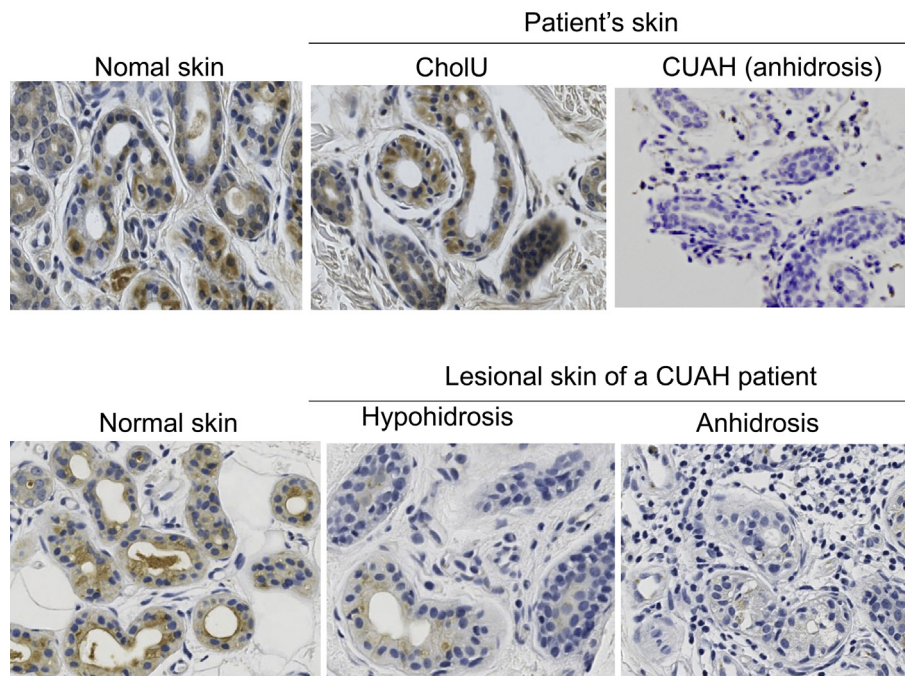


Fig. 4. Expression of CHRM3 in eccrine gland epithelial cells. Upper panel: Sections from skin of a normal subject (left), non-anhidrotic/hypohidrotic CholU (middle), and CUAH (anhidrotic area; right) were immunohistochemically stained with anti-CHRM3 antibody. The expression is impaired in CUAH. Lower panel: Sections from normal skin (left), CUAH hypohidrotic area (middle), and CUAH anhidrotic area (right) were immunostained for CHRM3. CHRM3 expression is reduced moderately in the hypohidrotic area and completely in the anhidrotic area.

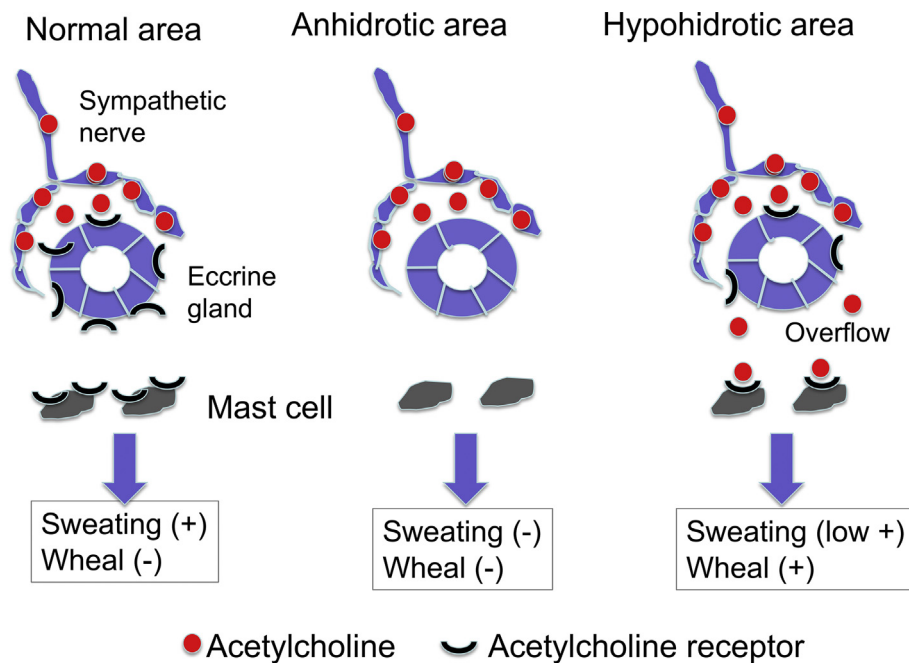


Fig. 5. Mechanism of wheal formation in CUAH. Wheal occurs in the hypohidrotic area presumably because of overflow of Ach to mast cells infiltrating in the vicinity of sweat glands.

only the sweat allergic type but also the depressed sweating type, i.e. CUAH or AIGA. The atopic property of CUAH/AIGA is supported by the finding that 43% cases of AIGA had elevated serum IgE levels.¹⁹ In our immunohistochemical study, the expressions of T cell/mast cell-attracting chemokines, CCL2/MCP-1, CCL5/RANTES and CCL17/TARC^{29,30} are elevated in the eccrine epithelial cells of CUAH. The accumulated T cells may affect the expression of CHRM3 and Ach esterase, and the chemoattracted mast cells may participate in wheal formation.²⁶ Accordingly, atopic dermatitis lesional skin shares the expression pattern of these chemokines with CUAH.²⁶

Treatments of CholU

CholU is different from chronic spontaneous urticaria in the treatment responsiveness, as the therapeutic effects of second-generation antihistamines are insufficient in two-third of the patients with CholU.³¹ In a case study, additional efficacy of lafutidine was reported.³² Meanwhile, alleviation of intractable pain by risperidone was documented in a patient with AIGA.³³ Recently, omalizumab, a novel humanized monoclonal anti-IgE antibody, is used for refractory CholU with a good therapeutic effect.^{34,35} Participation of IgE in the pathogenesis of CholU is an interesting issue in future.

For CUAH, one of the first line treatments is the pulse therapy with a high dose of corticosteroid.²⁰ The therapy is usually repeated three or more times, depending on the efficacy of individual patients. This systemic therapy improves urticaria as well as perspiration.²⁰ Since corticosteroids inhibit the expression of CCL2, CCL5 and CCL17,³⁶ they can depress T cell infiltration and allow CHRM3 to re-express on the epithelial cells. Two Japanese patients with CUAH had episodes of seizures concomitantly with wheals.³⁷ Given that Ach mediates epileptic seizures,³⁸ it is hypothesized that convulsion is evoked via Ach receptors that are re-expressed in the brain during corticosteroid administration.

Complications of ach-directly induced, depressed sweating type (CUAH)

There have been reported various conditions that are complicated with CUAH or AIGA. A review of literature revealed that seven cases of AIGA were accompanied by central diabetes insipidus (DI), a disease caused by antidiuretic hormone deficiency.^{40,41} One of the causes of central DI is lymphocytic infundibulo-hypophysitis, which is estimated as an autoimmune disorder⁴² and was documented in some cases of AIGA with central DI.³⁹ Other autoimmune diseases that are associated with AIGA include alopecia areata, rheumatoid arthritis, and vitiligo vulgaris.³⁹ These observations support the notion that CUAH/AIGA is induced by autoimmune T cell reactions. On the other hand, it has been found that anti-CHRM3 antibodies were detected in one of 12 cases of AIGA patients.⁴² Thus, in addition to autoreactive T cells, autoantibodies to the Ach receptor might play a causative role for the depressed perspiration. The effectiveness of corticosteroids may be due to depression of these immunological reactions. Interestingly, a review of literature revealed that there have been 19 Japanese cases of Sjögren's syndrome with generalized or segmental anhidrosis,⁴³ further suggesting an autoimmune mechanism underlying depressed perspiration.

Conclusions

Ach mediates CholU, but the action of Ach is different between the subtypes of CholU. Both direct and indirect actions of Ach operate in the development of CholU. These modes of action are related to perspiration. We propose that CholU can be categorized into two major subtypes: Ach-indirectly induced, sweat allergic type and Ach-directly induced, depressed sweating type. The latter subtype is also known as CUAH/AIGA and may be an autoimmune condition. This categorization would be helpful for better understanding of CholU.

Other distinct types of CholU have been noticed. Angioedema,⁴⁴ in particular, palpebral angioedema⁴⁵ occasionally occurs in

patients with ChIU. Anaphylaxis is another complication with ChIU.⁴⁶ In addition, combination of ChIU and cold urticaria was documented.⁴⁷ Future studies are required to further categorize these conditions.

Conflict of interest

The author has no conflict of interest to declare.

References

- Hirschmann JV, Lawlor F, English JS, Louback JB, Winkelmann RK, Greaves MW. Cholinergic urticaria. A clinical and histologic study. *Arch Dermatol* 1987;**123**: 462–7.
- Black AK, Lawlor F, Greaves MW. Consensus meeting on the definition of physical urticarias and urticarial vasculitis. *Clin Exp Dermatol* 1996;**21**:424–6.
- Tokura Y. New etiology of cholinergic urticaria. In: Yokozeki H, Murota H, Katayama I, editors. *Perspiration Research. Current Problems in Dermatology*, Vol. 51. Basel: Karger; 2016. p. 94–100.
- Bito T, Sawada Y, Tokura Y. Pathogenesis of cholinergic urticaria in relation to sweating. *Allergol Int* 2012;**61**:539–44.
- Fantozzi R, Masini E, Blandina P, Mannaioni PF, Bani-Sacchi T. Release of histamine from rat mast cells by acetylcholine. *Nature* 1978;**273**:473–4.
- Blandina P, Fantozzi R, Mannaioni PF, Masini E. Characteristics of histamine release evoked by acetylcholine in isolated rat mast cells. *J Physiol* 1980;**301**: 281–93.
- Sawada Y, Nakamura M, Bito T, Fukamachi S, Kabashima R, Sugita K, et al. Cholinergic urticaria: studies on the muscarinic cholinergic receptor M3 in anhidrotic and hypohidrotic skin. *J Invest Dermatol* 2010;**130**:2683–6.
- Adachi J, Aoki T, Yamatodani A. Demonstration of sweat allergy in cholinergic urticaria. *J Dermatol Sci* 1994;**7**:142–9.
- Kobayashi H, Aiba S, Yamagishi T, Tanita M, Hara M, Saito H, et al. Cholinergic urticaria, a new pathogenic concept: hypohidrosis due to interference with the delivery of sweat to the skin. *Dermatology* 2002;**204**:173–8.
- Kim JE, Jung KH, Cho HH, Kang H, Park YM, Park HJ, et al. The significance of hypersensitivity to autologous sweat and serum in cholinergic urticaria: cholinergic urticaria may have different subtypes. *Int J Dermatol* 2015;**54**: 771–7.
- Hiragun T, Hiragun M, Ishii K, Kan T, Hide M. Sweat allergy: extrinsic or intrinsic? *J Dermatol Sci* 2017;**87**:3–9.
- Oda Y, Washio K, Fukunaga A, Imamura S, Hatakeyama M, Ogura K, et al. Clinical utility of the basophil activation test in the diagnosis of sweat allergy. *Allergol Int* 2020;**69**:261–7.
- Fukunaga A, Bito T, Tsuru K, Oohashi A, Yu X, Ichihashi M, et al. Responsiveness to autologous sweat and serum in cholinergic urticaria classifies its clinical subtypes. *J Allergy Clin Immunol* 2005;**116**:397–402.
- Takahagi S, Tanaka T, Ishii K, Suzuki H, Kameyoshi Y, Shindo H, et al. Sweat antigen induces histamine release from basophils of patients with cholinergic urticaria associated with atopic diathesis. *Br J Dermatol* 2009;**160**:426–8.
- Yamaga K, Murota H, Tamura A, Miyata H, Ohmi M, Kikuta J, et al. Claudin-3 loss causes leakage of sweat from the sweat gland to contribute to the pathogenesis of atopic dermatitis. *J Invest Dermatol* 2018;**138**:1279–87.
- Hiragun T, Ishii K, Hiragun M, Suzuki H, Kan T, Mihara S, et al. Fungal protein MGL₁₃₀₄ in sweat is an allergen for atopic dermatitis patients. *J Allergy Clin Immunol* 2013;**132**:608–15.
- Hiragun M, Hiragun T, Ishii K, Suzuki H, Tanaka A, Yanase Y, et al. Elevated serum IgE against MGL₁₃₀₄ in patients with atopic dermatitis and cholinergic urticaria. *Allergol Int* 2014;**63**:83–93.
- Itakura E, Urabe K, Yasumoto S, Nakayama J, Furue M. Cholinergic urticaria associated with acquired generalized hypohidrosis: report of a case and review of the literature. *Br J Dermatol* 2000;**143**:1064–6.
- Nakazato Y, Tamura N, Ohkuma A, Yoshimaru K, Shimazu K. Idiopathic pure sudomotor failure: anhidrosis due to deficits in cholinergic transmission. *Neurology* 2004;**63**:1476–80.
- Kuriyama S, Aoshima M, Tokura Y. [Investigation on depressed sweating and therapeutic responses to corticosteroid pulse therapy in 7 cases of AIGA/ cholinergic urticaria with anhidrosis and hypohidrosis]. *[Jpn J Dermatol]* 2016;**126**:1263–71 (in Japanese).
- Tong LJ, Balakrishnan G, Kochan JP, Kinét JP, Kaplan AP. Assessment of autoimmunity in patients with chronic urticaria. *J Allergy Clin Immunol* 1997;**99**: 461–5.
- Shelly WB, Shelly ED, Ho AK. Cholinergic urticaria: acetylcholine-receptor-dependent immediate-type hypersensitivity reaction to copper. *Lancet* 1983;**16**:843–6.
- Baron B, Schreiber G, Sokolovsky M. Cholinergic urticaria, copper-induced hypersensitivity, and muscarinic receptor. *Lancet* 1983;**2**:55.
- Haustein UF, Schliebs R, Schaller J. Changes in muscarinic acetylcholine receptor binding in skin slices of cholinergic urticaria. *Acta Derm Venereol* 1990;**70**:208–11.
- Magnus IA, Thompson RH. Cholinesterase levels in the skin in cholinergic urticaria and pruritus. *Br J Dermatol* 1956;**68**:283–9.
- Sawada Y, Nakamura M, Bito T, Sakabe J, Kabashima-Kubo R, Hino R, et al. Decreased expression of acetylcholine esterase in cholinergic urticaria with hypohidrosis or anhidrosis. *J Invest Dermatol* 2014;**134**:276–9.
- Tsuchiya T, Aoyama K, Hasegawa M, Tamura A, Ishikawa O. [Cholinergic urticaria associated with hypohidrosis improved after admission]. *[Jpn J Clin Dermatol]* 2004;**58**:129–31 (in Japanese).
- Takahagi S, Tanaka T, Ishii K, Suzuki H, Kameyoshi Y, Shindo H, et al. Sweat antigen induces histamine release from basophils of patients with cholinergic urticaria associated with atopic diathesis. *Br J Dermatol* 2008;**160**: 426–8.
- Conti P, Pang X, Boucher W, Letourneau R, Reale M, Barbacane RC, et al. Impact of Rantes and MCP-1 chemokines on in vivo basophilic cell recruitment in rat skin injection model and their role in modifying the protein and mRNA levels for histidine decarboxylase. *Blood* 1997;**89**:4120–7.
- Tsunemi Y, Saeki H, Nakamura K, Nagakubo D, Nakayama T, Yoshie O, et al. CCL17 transgenic mice show an enhanced Th2-type response to both allergic and non-allergic stimuli. *Eur J Immunol* 2006;**36**:2116–27.
- Mellerowicz E, Weller K, Zuberbier T, Maurer M, Altrichter S. Real-life treatment of patients with cholinergic urticaria in German-speaking countries. *J Dtsch Dermatol Ges* 2019;**17**:1141–7.
- Hatakeyama M, Fukunaga A, Washio K, Ogura K, Yamada Y, Horikawa T, et al. Addition of lufutidine can improve disease activity and lead to better quality of life in refractory cholinergic urticaria unresponsive to histamine H1 antagonists. *J Dermatol Sci* 2016;**82**:137–9.
- Aoshima M, Suzuki Y, Masuda Y, Yoshinari Y, Hashizume H, Tokura Y. Successful treatment of chronic intractable pain with risperidone in a patient with acquired idiopathic generalized anhidrosis. *J Dermatol* 2018;**45**: e189–90.
- Gastaminza G, Azofra J, Nunez-Cordoba JM, Baeza ML, Echechipia S, Gaig P, et al. Efficacy and safety of Omalizumab (Xolair) for cholinergic urticaria in patients unresponsive to a double dose of antihistamines: a randomized mixed double-blind and open-label placebo-controlled clinical trial. *J Allergy Clin Immunol Pract* 2019;**7**:1599–609.
- Ihishashi-Kunimi Y, Imafuku S. Cholinergic urticaria with hypohidrosis successfully treated with omalizumab. *J Dermatol* 2020;**47**:e47–8.
- Hoshino M, Nakagawa T, Sano Y, Hirai K. Effect of inhaled corticosteroid on an immunoreactive thymus and activation-regulated chemokine expression in the bronchial biopsies from asthmatics. *Allergy* 2005;**60**:317–22.
- Takezaki S, Suzuki D, Kida K, Sato T, Uetake K, Sageshima S, et al. [A case of cholinergic urticaria with epileptic seizure and abnormalities on electroencephalogram]. *J Obihiro Kosei Gen Hospital* 2003;**6**:145–7 (in Japanese).
- Whalley BJ, Postlethwaite M, Constanti A. Further characterization of muscarinic agonist-induced epileptiform bursting activity in immature rat piriform cortex, *in vitro*. *Neuroscience* 2005;**134**:549–66.
- Imura K, Kasuya A, Tokura Y. Acquired idiopathic generalized anhidrosis: a case accompanied by central diabetes insipidus. *J Vis Dermatol* 2020;**19**:237–9.
- Shimizu H, Obi T, Miyajima H. Anhidrosis: an unusual presentation of diabetes insipidus. *Neurology* 1997;**49**:1708–10.
- Yasuda Y, Iwama S, Kiyota A, Izumida H, Nakashima K, Iwata N, et al. Critical role of rabphilin-3A in the pathophysiology of experimental lymphocytic neurohypophysitis. *J Pathol* 2018;**244**:469–78.
- Asahina M, Sano K, Fujinuma Y, Kuwabara S. Investigation of antimuscarinic receptor autoantibodies in patients with acquired idiopathic generalized anhidrosis. *Intern Med* 2013;**52**:2733–7.
- Takayanagi Y, Kageyama R, Aoshima M, Gujiyama T, Tokura Y. Generalized anhidrosis: a case accompanied by Sjögren's syndrome. *J Vis Dermatol* 2020;**19**: 240–2.
- Mellerowicz EJ, Asady A, Maurer M, Altrichter S. Angioedema frequently occurs in cholinergic urticaria. *J Allergy Clin Immunol Pract* 2019;**7**:1355–7.
- Washio K, Fukunaga A, Onodera M, Hatakeyama M, Taguchi K, Ogura K, et al. Clinical characteristics in cholinergic urticaria with palpebral angioedema: report of 15 cases. *J Dermatol Sci* 2017;**85**:135–7.
- Vadas P, Sinilaite A, Chaim M. Cholinergic urticaria with anaphylaxis: an underrecognized clinical entity. *J Allergy Clin Immunol Pract* 2016;**4**: 284–91.
- Tanaka M, Nakagawa Y, Hayashi M, Kotobuki Y, Katayama I, Fujimoto M. A case of cold-induced cholinergic urticaria accompanied by cholinergic urticaria showing a positive ice cube test. *Allergol Int* 2020;**69**:150–1.