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Invited review article

Sweat, the driving force behind normal skin: An emerging perspective on functional biology and regulatory mechanisms

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ABSTRACT

The various symptoms associated with excessive or insufficient perspiration can significantly reduce a patient's quality of life. If a versatile and minimally invasive method could be established for returning sweat activity to normalcy, there is no question that it could be used in the treatment of many diseases that are believed to involve perspiration. For this reason, based on an understanding of the sweat-gland control function and sweat activity, it was necessary to conduct a comprehensive search for the factors that control sweating, such as the central and peripheral nerves that control sweat-gland function, the microenvironment surrounding the sweat glands, and lifestyle. We focused on the mechanism by which atopic dermatitis leads to hypohidrosis and confirmed that histamine inhibits acetylcholinergic sweating. Acetylcholine promotes the phosphorylation of glycogen synthesis kinase 3β (GSK3β) in the sweat-gland secretory cells and leads to sensible perspiration. By suppressing the phosphorylation of GSK3β, histamine inhibits the movement of sweat from the sweat-gland secretory cells through the sweat ducts, which could presumably be demonstrated by dynamic observations of the sweat glands using two-photon microscopy. It is expected that the discovery of new factors that control sweat-gland function can contribute to the treatment of diseases associated with dyshidrosis.

Contents

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1. Introduction

The symptoms associated with abnormalities such as excessive or insufficient perspiration can significantly reduce a patient's quality of personal and social life. For example, individuals with anhidrosis suffer from increased body temperature, skin dryness, and tingling sensations in warmer circumstances [1,2]. There is no established treatment regimen for anhidrosis, and although methods, such as steroid pulse therapy, have been attempted in severe cases, treatments have developed slowly for mild to moderate anhidrosis associated with subjective symptoms [2,3]. It can be mentioned that the background factors in anhidrosis that could serve as a framework for establishing treatment methods have not been fully elucidated. It was necessary to conduct a comprehensive search for the factors that control sweating, such as the central and peripheral nerves controlling sweat-gland function, the microenvironment surrounding the sweat glands, and lifestyle.

2. The basis of sweating

2.1. The function of sweat

The hydrolipidic film, formed by mixing sweat and sebum, covers the skin surface forming a protective wall, which is the skin's front-line barrier [4]. In addition to protecting the organism from dry environments by preventing the evaporation of moisture from the body [5], the sebum film promotes the growth of normal microflora [6]. Sweat is not only a constituent of the sebum film, it participates in thermoregulation, exerts a moisturizing effect on the surface of the skin, and contains antimicrobial peptides (AMPs; e.g., dermcidin and cathelicidin) and secretory IgA, which act to defend against infection [7–9]. For this reason, sweat is indispensable in maintaining skin homeostasis.

Thus, sweat composition greatly influences the homeostasis of skin in diverse ways. Sato defined sweat as a dilute electrolyte solution that contains mainly NaCl, K, and bicarbonate (HCO_3). Besides AMPs, other included substances, such as lactate and urea, regulate the retention of the stratum corneum. Lactate is a glycolysis metabolite and is known to increase in oxidative stress, physical exertion, and metabolic stress [10]. Dobson and Sato [11] confirmed that both lactate and CO_2 were produced from isolated eccrine sweat glands incubated with glucose. Moreover, the lactate concentration in sweat is higher than that in plasma (about 2 mM and 10–15 mM, respectively) [12,13], indicating that anaerobic and aerobic glycolysis occur in the sweat gland itself. To support of this, Watabe et al. [14] confirmed the decreased lactate content in stratum corneum derived from lesional skin with anhidrosis. Lactate derived from sweat may regulate the desquamation of the stratum corneum [15] and may recover the water-retaining capacity of the stratum corneum [16]. In contrast, sweat contains as much urea as plasma does [15]. Urea also may have role in the retention of the stratum corneum, like lactate [15].

Intertriginous body areas (e.g., axilla, inguinal, cubital fossa, and popliteal fossa), in other words, sweat-collecting areas, are known to be susceptible to sweat-related skin disorders. It could be thought that highly concentrated lactate and urea in neglected sweat adversely affects the retention of the stratum corneum.

2.2. The physiological and anatomical characteristics of sweating

Physiological sweating is produced mainly by the eccrine sweat glands, which have the ability to secrete large amounts of sweat. The main structural feature is the secretory gland surrounded by myoepithelial cells (Fig. 1A). Eccrine sweat glands receive cholinergic sympathetic innervation, and the nerve fibers are distributed in the form of a mesh around the gland body [17] (Fig. 1B). Sweat secretion is subject to humoral control. Sweating is induced by acetylcholine and inhibited by atropine. Also, to cope with the high secretory capacity, blood vessels are distributed abundantly in the vicinity of the gland body and the ducts [17] (Fig. 1B and C). The blood vessels surrounding the vicinity of the ducts are involved in the reabsorption of HCO_3^- and NaCl from the ducts [15,17] (Fig. 1C). The eccrine sweat glands are distributed throughout almost the entire body and are said to number from 2,000,000 to 5,000,000 per person [17]. The number of eccrine sweat glands remains unchanged during growth, and the density is affected by the body's surface area [17]. For this reason, the density of eccrine sweat glands in infants is sevenfold or greater than that in adults. Conceivably, the impact of sweat on the skin will change with age.

In addition, there are eccrine sweat glands with sweating ability (active sweat glands) and without (inactive sweat glands) [17]. The development of the eccrine sweat glands starts at 28 weeks of gestation and an increase in active-to-inactive ratio of sweat glands ends at the age of 2.5 years [17]. The degree of activation is affected by the thermal environment during this period. This means that the proportion of active sweat glands is smaller for those born in cold climates and greater for those born in the tropics [17]. There are concerns about the effects of indoor environments controlled by air conditioning on sweating ability. Insufficient development of the sweating function during early childhood can easily set the stage for impaired skin homeostasis.

Furthermore, sweat volume undergoes drastic age-related changes [17,18]. Infants sweat less [17]. After early childhood, apparent sweating is found. The sweat volume increases drastically with increasing age and peaks at about 12 years of age (Fig. 1D) [17,18]. At about 14–16 years of age, sweating activity gradually decreases and stabilizes to become equivalent to that of adults (Fig. 1D) [17,18].

2.3. The mechanisms of sweat secretion and reabsorption

The molecular mechanisms of sweat secretion have been partly elucidated (Fig. 2A) [15,19,20]. Cholinergic stimulation via acetylcholine receptor (AchR) generates inositol 1,4,5-triphosphatase (IP_3) in the cytosol. IP_3 leads to Ca^+ release from the endoplasmic reticulum (ER) and increases the intracellular Ca^+ concentration. The increased cytoplasmic Ca^+ concentration promotes ion influx, ion outflow, and H_2O egestion (Fig. 2A). In the process of ion outflow, the activation of cystic fibrosis transmembrane conductance regulator (CFTR), a plasma membrane cAMP-activated Cl^- channel, by a set of processes is important. Activated protein kinase C (PKC) interacts with ezrin, a molecular switch, and promotes the dimerization of CFTR. This process facilitates the efficient phosphorylation of CFTR by protein kinase A (PKA). Adrenergic stimulation via adrenaline receptors also induces sweating. cAMP plays the role of the messenger of adrenergic sweating by activating PKA [15,21]. Cholinergic stimulation also alters de novo glycogen synthesis by the phosphorylation of glycogen synthesis kinase 3β (GSK3β) [20]. This process is thought to contribute to perceptible sweat secretion.

Regarding ionic migration, an Na-K-Cl cotransport model of secretory portion of the sweat gland has been proposed (Fig. 2B, left). Sudomotor stimulation, including acetylcholine (Ach), increases Ca^{2+} entry into the cell and promotes the permeability of the basolateral plasma membrane to Na^+. The Na-K-Cl cotransporter (NKCC1) and a Na^+ pump are located on the basolateral plasma membrane of the sweat secretory cells [15,22]. Influent Na^+ is partly pumped out by the Na^+ pump,