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Pathophysiology of Sweating

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Generalized eccrine sweating is the physiological response to an increased body temperature during physical exercise or following thermal stress, and it is the most effective means by which humans regulate their body temperature through evaporative heat loss. Exaggerated local systemic sweating responses result in hyperhidrosis, which is not only unpleasant, but impairing social and occupational activities.

About 3 million eccrine sweat glands are distributed over nearly the entire body surface. A well-acclimatized person can produce as much as several litres of sweat per hour and 10 litres per day. The secretory activity of the human eccrine sweat gland fulfils two major functions: (1) secretion of an ultrafiltrate of a plasma-like precursor fluid by the secretory coil in response to acetylcholine that is released from the sympathetic nerve endings and (2) reabsorption of sodium in excess of water by the duct, thereby producing hypertonic skin surface sweat. The ductal reabsorptive function is vital to the conservation of electrolytes in the body. In addition to the secretion of water and electrolytes, sweat contains heavy metals, organic compounds and macromolecules.

Thermoregulation

To keep the body temperature constant, the thermoregulatory centre located in the hypothalamus receives information from inner thermosensors about the core temperature and from outer thermosensors perceiving skin temperature and muscle activity. Effector systems adjusting the body temperature are metabolic and muscular activity, blood vessels of the skin and eccrine sweat glands. Endogenous production of heat is the consequence of general metabolic activity of the body. Blood supply to the skin regulates the convective heat

resistance of the periphery, whereby an increased blood circulation through the skin increases the heat transport to the body surface and a reduced thermal blood flow decreases the heat convection from the body core to the body surface. Finally, sweating generates evaporative heat loss from the body surface dissipating it to the environment [25].

Several factors modify thermoregulation in the hypothalamic centre. These include hormones, pyrogens, physical activity and emotional stimuli. Proteins or lipopolysaccharides of bacteria and viruses act directly as pyrogens. Endotoxins release endogenous pyrogens from leucocytes and cells of the reticuloendothelial system. Temperature changes during the menstrual cycle as well as thermoregulatory imbalances during the climacterium are not completely understood. Via the limbic system, emotional and physical activity influences the thermoregulatory centre. The great variety of factors possibly influencing the thermoregulatory system explains the multitude of possibilities able to modify the actual threshold for eccrine secretion [27].

Mechanism of Sweat Secretion

The concept of the ionic mechanism of fluid secretion in exocrine glands has emerged during the past decades. It has replaced the former Ussing's leak pump model [48, 49]. Sato [39] has proposed a modification of the Na-K-2Cl cotransporter model, as it was postulated in Ehrlich ascites tumour cells [13] to explain the mechanism of sweat secretion by the clear cells of the eccrine acini. Acetylcholine released from periglandular cholinergic nerve endings in response to nerve impulses binds to cholinergic receptors, presumably present in the basolateral membrane of the clear cell. The activation of these receptors stimulates an influx of extracellular Ca into the cytoplasm (fig. 1). The increased intracellular [Ca] stimulates Cl channels in the luminal membrane and K channels in the basolateral membrane, causing a net KCl efflux from the cell. Consequently, cell volume decreases because water follows the solutes to maintain iso-osmolarity; the cell shrinks. The decrease in [K] and [Cl] provides a favourable chemical potential gradient, probably the driving force, for Na-K-2Cl cotransporters located in the basolateral membrane. The cotransporters carry Na^+, K^+ and $2Cl^-$ into the cell in an electrically neutral fashion. Since Na channels are absent in the clear cell membrane, Na-K-2Cl cotransporters are the only means by which Na enters the cells. The increase in cytoplasmic [Na] is well known to stimulate Na pumps, which extrude cytoplasmic Na in exchange for extracellular K but, since the Na-K-2Cl cotransporters are continuously operating, [Na] remains higher than the prestimulation level. In the steady state of secretion, K and Na recycle across the basolateral membrane without further loss. In contrast, Cl enters the cell via Na-K-2Cl cotransporters and moves into the lumen through

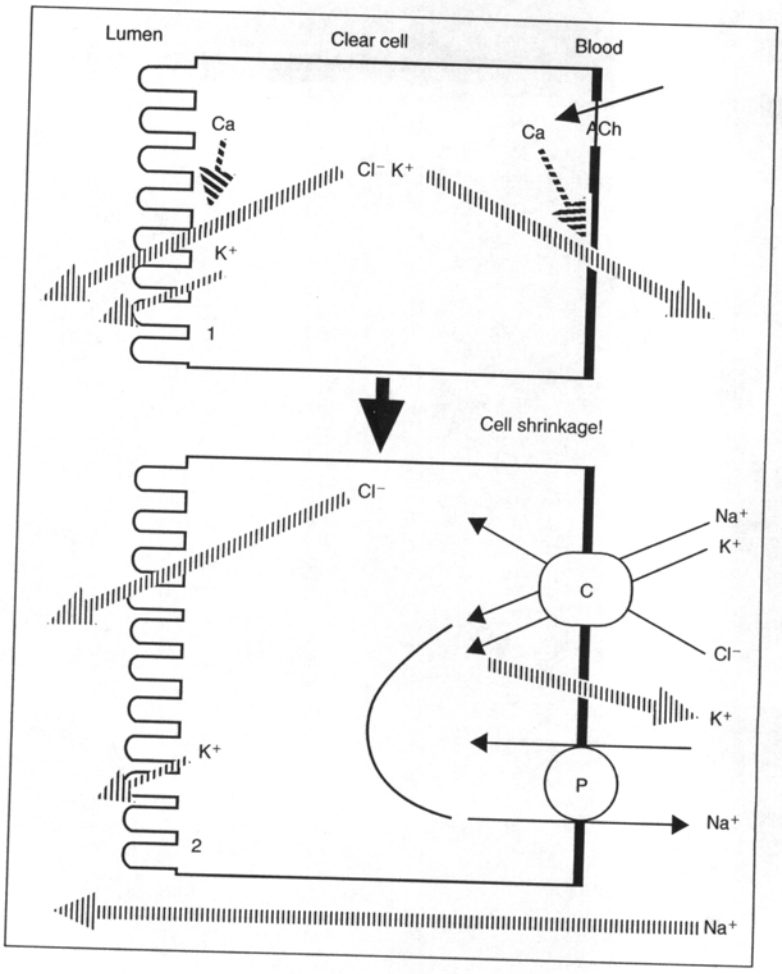

Fig. 1. Modified Na-K-2Cl cotransporter model for the mechanism of eccrine sweat secretion (modified from Sato [39]). C = Na-K-2Cl cotransporter; P = Na^+-K^+-ATPase-dependent Na pump.

the Cl channels at the apical membrane. The movement of Cl across the apical (luminal) membrane, which is down the electrochemical gradient, depolarizes the apical membrane and generates the negative luminal potential. This luminal negative potential then attracts Na into the lumen across the Na-conductive intercellular junction. Thus, the Na and the Cl that enter the lumen across the cell join into the lumen to form NaCl in the isotonic primary fluid.

In the coiled portion of the sweat duct, reabsorption of NaCl occurs to preserve electrolytes creating the hypotonic sweat, which is secreted to the skin

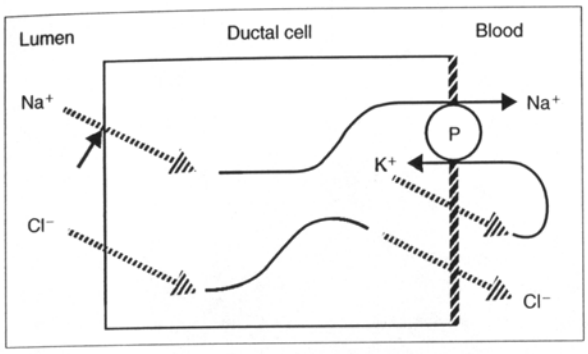

Fig. 2. Mechanism of reabsorption of electrolytes from primary eccrine sweat in the distal portion of the secretory acini (modified from Sato [39]). P = Na^+-K^+-ATPase-dependent Na pump.

surface [39]. The absorption of NaCl by the duct is due to the active transport of Na ions by the Na pump located in the basal ductal cell membrane (fig. 2). Chloride is also transported against the chemical gradient but down a favourable electrical gradient. It is widely accepted that the transport mechanism of the sweat duct largely conforms to Ussing's leak pump model. In cystic fibrosis, Cl channels in the luminal membrane are defective and those in the basal membrane are significantly decreased resulting in excess Cl^- in the sweat secreted onto the surface.

Pathogenesis of Hyperhidrosis

Hyperhidrosis may be categorized as physiological, symptomatic or idiopathic [23]. It may be generalized or focal. Causes of symptomatic hyperhidrosis include endocrinological disorders (hyperpituitarism, hyperthyroidism), disorders with elevated catecholamines (shock, hyperglycaemia, phaeochromocytoma) and neurological disorders (damage to sympathetic nerves, auriculotemporal syndrome, diabetic neuropathy). Emotionally triggered sweating in hyperhidrosis axillaris, manuum or pedum belongs, as well as gustatory sweating without neurological disorders, to the idiopathic types of hyperhidrosis. Excessive sweating occurs physiologically during acclimatization and in postmenopausal women (table 1).

Physiological Hyperhidrosis

In acclimatization, several measurable changes occur in eccrine glands. The susceptibility of the eccrine glands to secretory stimuli is increased. Sweating is optimized with regard to quantity of secretion and reabsorption of electrolytes.

Table 1. Pathogenesis of hyperhidrosis

Causative disorder	Example
Physiological hyperhidrosis	Acclimatization Menopause Idiopathic gustatory sweating
Endocrinological disorders	Hyperpituitarism Hyperthyroidism
Elevated catecholamines	Hypoglycaemia Shock Phaeochromocytoma
Neurological disorders	Cervical rib Carpal-canal syndrome Auriculotemporal syndrome and other types of symptomatic gustatory sweating Tabes dorsalis Syringomyelia Encephalitis Diabetic neuropathy Hemiplegia Plexus lesions Sympathetic chain lesions
Compensatory hyperhidrosis in association with widespread anhidrosis	Ross syndrome Diabetic neuropathy Miliaria Sympathetic chain lesions
Axon reflex sweating	Inflammatory skin lesions
Naevoid disorder	Naevus sudoriferus
Idiopathic hyperhidrosis	Hyperhidrosis axillaris Hyperhidrosis manuum Hyperhidrosis pedum

Secretion is reduced to the amount of sweat which can just evaporate from the skin surface. Profuse sweating is, therefore, prevented and despite the optimal cooling effect, the skin remains dry. Simultaneously, reabsorption of electrolytes is increased to minimize the loss of viable ions [35]. Acclimatization means adaptation, a process which can be trained.

Postmenopausal women tend to sweat profusely in association with flushes. Metabolites of hormones seem to play a role; the mechanisms may be similar to changes in the hormone-regulatory centre, during the menstrual cycle. Susceptibility of eccrine glands to other sudomotor stimuli may be enhanced, and for that reason sweat production appears inadequately overshooting.

The distribution pattern of sweating simulates the thermoregulatory type of sweating. An increased incidence of localized axillary or palmoplantar sweating does not seem to occur among postmenopausal women.

Endocrinological Causes of Hyperhidrosis

Hyperpituitarism

Increased release of metabolic hormones, e.g. in hypophyseal adenomas, leads to increased metabolic activity and associated heat production. As a consequence, thermoregulatory sweating is induced. This is the reason why acromegalic patients sometimes seek medical aid to treat disturbingly increased sweating [33]. Treatment with a long-acting somatostatin analogue induces suppression of growth hormone and also induces relief of hyperhidrosis [45].

Hyperthyroidism

Increased sweating is regarded as a common symptom of thyroid hyperfunction. Increased susceptibility of eccrine glands to secretory stimuli, however, has not been found in hyperthyroid patients [2, 14]. In addition, idiopathic hyperhidrosis of the axillae, palms and soles is almost never associated with hyperthyroidism. Increased metabolic activity in response to hyperfunction of the thyroid gland increases heat production, and consequently sweating is induced. On the other hand, hyperhidrosis as a disturbing symptom almost never leads to the diagnosis of hyperthyroidism.

Elevated Release of Catecholamines

An important symptom for the diagnosis of hypovolaemic shock or hypoglycaemia is cold sweat on the forehead of the patient. In both situations, as in the rare case of a phaeochromocytoma, catecholamines are released in excess. Although there are indications for a direct pharmacological stimulation of eccrine acini by adrenaline and noradrenaline [9, 52], a central effect of catecholamines seems to be the cause of sweating in the above-mentioned disorders. Since peripheral vasoconstriction is associated with the release of catecholamines, skin temperature remains low and the sweat feels cold.

Neurological Disorders Associated with Hyperhidrosis

Central or Peripheral Nerve Lesions

In general, incomplete lesions of the peripheral sudomotor nerves may lead to hyperhidrosis; complete disruption results in anhidrosis. The distribution

patterns of disturbances of sweat function are indicative of the location of the dysfunction. Segmental hyperhidrosis has been described in cases with spinal and paraspinal disease [41] and in patients with the rare Chiari type I malformation [46]. Posttraumatic syringomyelia induced hyperhidrosis affected by posture [16]. Accessory cervical ribs may cause segmental hyperhidrosis on the face, neck and shoulder due to damage of the cranial part of the sympathetic chain [11]. The palm is affected in the carpal-canal syndrome. Bizarre distribution patterns emerge in tabes dorsalis, syringomyelia or encephalitis. In such patients, hemilateral or unilateral segmental hyperhidrosis has been described on the head [5, 50]. Acute hemispherical brain infarction and lateral medullary infarcts also lead to hyperhidrosis [38]. In medullary infarcts it was observed contralaterally, and in hemiparetic stroke hyperhidrosis was confined to the paretic side [26]. In reflex sympathetic dystrophy (Sudeck syndrome), hyperhidrosis of the affected limb is also a characteristic symptom [36]. The pathogenesis of hyperhidrosis associated with episodic spontaneous hypothermia is unknown [44]. It is hypothesized that a specific serotonergic dysfunction of the anterior hypothalamus is involved in this condition.

Sympathetic Nerve Lesions

Disruption of central sympathetic fibres between the hypothalamus and medulla leads to an ipsilateral complete anhidrosis. Transverse lesions above the second lumbar segment result in complete anhidrosis of the depending skin areas. Complete lesions of the sympathetic chain lead to widespread segmental anhidrosis, sometimes of complete body quadrants. If anhidrotic areas are large enough to interfere with thermoregulation, disturbing compensatory hyperhidrosis can occur in the remaining fully innervated skin areas [37, 47]. This is also observed in widespread diabetic neuropathy, in Ross syndrome, and after therapeutic sympathectomy for localized hyperhidrosis [3, 28, 40].

Gustatory Sweating

A special type of neurological hyperhidrosis is gustatory sweating in auriculotemporal syndrome, first described by Frey [12] in 1923. After inflammatory processes or surgical procedures in the parotic area, regeneration of nerve fibres may lead to contact between secretory fibres of the nervus auriculotemporalis to sudomotor sympathetic fibres. As soon as salivation occurs during eating, simultaneous eccrine sweating is induced at the cheek or mandibular area. Surgery in the vicinity of the glandula mandibularis or sublingualis may lead to connection to salivator fibres of the chorda tympani and result in hyperhidrosis of the submental area [55]. After cervical and upper thoracic sympathectomy, very disturbing and vast segmental gustatory sweating has been described [7, 21]. Damage to the ganglion cervicale superior by diabetic neuropathy was

also found as the cause of gustatory sweating [42, 43, 52, 53]. These variants of gustatory sweating induced by neurological disturbances are associated with every salivary stimulus. This is not to be confused with the idiopathic type of gustatory sweating which occurs symmetrically only in conditioned individuals and following consumption of only certain types of food.

Axon Reflex Sweating

It occurs around the border of painful skin lesions, such as venous ulcers, under additional emotional stimuli. This phenomenon is based on a direct axon reflex and may be experimentally induced by injection of nicotinic acid [51]. A very peculiar finding was localized hyperhidrosis in a patient with pretibial myxoedema [15]. The pathogenesis in this case remained, however, unclear.

Naevus sudoriferus

There are several cases of localized hyperhidrosis without any relation to segmental or otherwise neurological distribution and in the absence of any neurological disorders. This type of localized hyperhidrosis occurs spontaneously following thermal or emotional stimuli [4, 17, 19, 29]. Topical pharmacological stimulation by cholinergics also led to an overshooting sweating response [10, 18, 32]. In most cases, histological examination revealed hyperplastic eccrine acini with only rarely increased numbers of sweat glands per skin area [4]. Lesions may be linear, nummular or palm sized and are mostly located on the face, upper trunk and, especially, the forearms. It is still under debate whether naevus sudoriferus represents a functional naevus with increased susceptibility to the sudomotor stimuli or an increase in numbers of sweat glands or, respectively, hyperplasia of sweat glands in normal numbers. It is also unclear, whether a primary functional naevus may lead to hypertrophic glands following continuous stimulation.

Idiopathic Hyperhidrosis

These are the classical types of localized hyperhidrosis known to the dermatologist. They comprise hyperhidrosis axillaris, hyperhidrosis manuum and hyperhidrosis pedum. Idiopathic hyperhidrosis is manifested in areas where sweating is induced mainly by emotional stimuli. The different types occur either simultaneously or in different combinations. In 256 patients, 115 exhibited hyperhidrosis axillaris, 86 hyperhidrosis manuum and 75 hyperhidrosis

pedum [23]. The most frequent manifestations were isolated hyperhidrosis axillaris, the combination of hyperhidrosis axillaris and palmoplantar hyperhidrosis, and isolated palmoplantar hyperhidrosis. During the course of their disorder, many patients complained about a tendency to progression to generalized and profuse sweating of the thermoregulatory type. It is, therefore, believed that emotionally triggered sweating is not always restricted to the palms, soles and axillae but may also spread to the forehead, capillitium and trunk, simulating the thermoregulatory pattern of sweating [2]. Hyperhidrotic patients experimentally show a reduced threshold for emotional sweating [1]. On the other hand, pharmacologically induced and thermoregulatory sweating types were found to be normal.

It is assumed that idiopathic hyperhidrosis is the result of hyperexcitability of the reflex circuits involved in eccrine secretion. This has recently been reinvestigated [31]. The sympathetic sudomotor skin response was found enhanced in hyperhidrotic patients as compared to controls. This hyperexcitability of the somatosympathetic polysynaptic pathway may partly explain the pathophysiology of idiopathic hyperhidrosis. Similarly, sympathetic nerve activities in the skin were found enhanced after mental and peroneal stimuli in patients with primary palmoplantar hyperhidrosis [24]. Further, in a group of 63 patients with idiopathic hyperhidrosis, the cardiac autonomic function was investigated by spectral analysis of heart rate variability [6]. Interestingly, differences in the response of the parasympathetic cardiac innervation were detected. This indicates a much more complex autonomic dysfunction than generalized sympathetic overactivity as the cause of focal hyperhidrosis.

The biological significance of emotional sweating may be seen in the context of an ergotropic sympathetic reaction induced by acute stress. In this view, emotional sweating represents an atavistic function important when hunting wild animals or combating human enemies. Sweating on palms and soles regulates the humidity of the stratum corneum and, in that way, optimizes friction. This guarantees a firm grip and a secure step. Generalized sweating cools down the body in anticipation of strenuous physical activity. If axillary odour is perceived as a physiological signal in the sense of pheromones, the quick onset of axillary eccrine sweating supports this function. Bacterial degradation of apocrine sweat generates odoriferous substances adhering to the surface of the skin and axillary hair [30]. These preformed natural fragrances are set free by evaporation of suddenly generated eccrine sweat.

Idiopathic hyperhidrosis mainly starts at puberty, reaches a peak in the third and fourth decades of life and decreases with older age. Hyperhidrosis axillaris is strongly associated with the reproductive age. Hyperhidrosis manuum and pedum frequently occurs in childhood or even in infancy. Hyperhidrosis axillaris seems to be more frequent and disturbing in women, hyperhidrosis

palmoplantaris seems to prevail in the male gender. Familial occurrence of idiopathic hyperhidrosis is frequent. Inheritance seems to be multifactorial and associated with the psychovegetative constitution of the individual [54].

Idiopathic hyperhidrosis mostly occurs spontaneously intermittently, induced by emotional stress. The threshold may be so low that normal daily activities are sufficient to maintain a continuous secretion. If hyperhidrosis is subjectively perceived as embarrassing, which is often the case in hyperhidrosis axillaris and hyperhidrosis manuum, a vicious circle is induced by the additional emotional stress. During sleep, emotional sweating is absent [20].

Hyperhidrosis is not only an embarrassing cosmetic problem but, in severe cases, an incapacitating disorder. Continuous wetness of clothing in axillary hyperhidrosis causes discolouration and finally destruction of fabrics. Maceration of the skin enhances growth of bacteria and fungi and forms the basis of intertrigo. Axillary bromhidrosis is a rather rare occurrence in hyperhidrotic patients, since the odoriferous metabolically formed constituents of apocrine sweat are flushed away by the continuous secretion of eccrine sweat. Plantar hyperhidrosis is less obvious, although destruction of footware may be very disturbing. Enhanced growth of bacteria leads to bromhidrosis and keratoma sulcatum (pitted keratolysis). A severe complication due to overgrowth by gram-negative bacteria is the macerative infection of the foot. Hyperhidrosis of the palms is subjectively most disabling. Shaking hands immediately discloses the problem. Papers are stained and corrosion occurs on metallic workpieces. These patients have become known as 'rusters' [8].

Simple Methods to Evaluate Hyperhidrosis

The severity of hyperhidrosis can easily be graded on a semiquantitative scale. In the axillary cavity, the staining of shirts or blouses may be used as a measure for severity. Normal axillary sweating generates small wet spots in the axilla not exceeding 5 cm. Stains between 5 and 10 cm and still confined to the armpit define mild hyperhidrosis (grade I). Stains between 10 and 20 cm may be considered as a sign of moderate hyperhidrosis (grade II). Sweat stains larger than 20 cm, sometimes reaching down to the waistline, are considered as a severe grade (grade III). Palmar hyperhidrosis of low grade is sharply confined to the palms, shows a moist skin surface but no visible sweat droplets (grade I). If the skin surface is very wet, some sweat drops become visible and sweating extends beyond the palm spreading to the distal dorsal phalanges, hyperhidrosis is considered moderate (grade II). If sweat drops off the palm and sweating spreads to the entire dorsal surface of the fingers, hyperhidrosis is severe (grade III) [22].

A simple way of objectively measuring sweat secretion and grading the intensity of hyperhidrosis is gravimetric measurement on the palms. After blotting the skin dry with a towel, the palms are brought into contact with preweighed paper sheets and kept in contact for 1 min. The absorbed sweat is then weighed by precise scales. Amounts not exceeding 20 mg/min/palm are considered as normal sweating. In extreme hyperhidrotic subjects, values exceeding 150 mg are frequently found [22].

A very quick technique to determine the skin area involved in hyperhidrosis is the starch-iodine method introduced by Minor [34]. A very practical modification of that method uses a mixture of 1.5% iodine solution and 10% castor oil in ethanol. The solution is painted on the skin surface which is to be evaluated. After drying, corn starch is dusted onto the skin and evenly distributed using a small brush. As soon as eccrine sweat reaches the skin surface, the light brown colour of the iodine solution turns deep purple by forming a coloured iodine-starch complex in the aqueous medium.

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