Review Article

Pathophysiology of hyperhidrosis

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Abstract: Primary hyperhidrosis is a pathologic condition that is characterized by excessive sweating beyond the physiological needs required for thermoregulation. It affects 0.6–5% of the world population and inflicts a significant impact on the quality of life in affected patients. The exact pathophysiology of primary hyperhidrosis remains unclear, but the prevailing theory of pathogenesis appears to be neurogenic hyper-excitability of the sympathetic nervous circuits innervating eccrine glands. In this paper, we aim to review the normal physiology of thermoregulation and discuss several theories and current evidence on the pathophysiological features of primary hyperhidrosis.

Keywords: Primary hyperhidrosis; pathophysiology; sweating; thermoregulation

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Introduction: hyperhidrosis

Primary or essential hyperhidrosis is a pathological disorder of unknown etiology, characterized by excessive and chronic perspiration that exceeds the physiological needs for a normal thermoregulation (1). In fact, it is an exaggerated response to physiological stress or emotional/psychological stimulus. Primary hyperhidrosis affects 0.6–5% of the world population and affects men and women equally (2). The onset of symptoms usually occurs before the age of 25 (3). Excessive sweat is localized and the anatomical regions mostly affected are palms, axillae, craniofacial region and soles of feet (2,4). An important aspect of primary hyperhidrosis is the occurrence of sweating episodes only when patients are awake (5) regardless of the environmental temperature.

Secondary hyperhidrosis is a generalized sweating disorder typically affecting the entire body, as a consequence of another underlying disorder, either metabolic, neoplastic, infectious or endocrine condition (4). Excessive perspiration can occur when patients are awake or sleeping and the onset of symptoms are usually in adulthood, coinciding with the onset of the underlying disorder in question (5). In addition, secondary hyperhidrosis can also be pharmacologically induced, with certain antidepressant medications (3,5).

Diagnosis is mainly clinical, with a thorough history and physical examination. Patient history should address disease onset, family history, pattern, triggers, severity and other associated symptoms (6). Hyperhidrosis Disease Severity Scale is an important tool in assessing the impact of disease in patients' daily activities. One such a scale by Strutton and colleagues, based on a US national survey, classifies sweating in 4 categories: never noticeable and never interfering with daily activities, tolerable but sometimes interfering, barely tolerable and frequently interfering, and intolerable and always interfering (6). A score of 3 or 4 indicates serious hyperhidrosis, which requires treatment. Hyperhidrosis can be diagnosed with a minor starch-iodine test, which is a semi-quantitative test that can be used for whole-body mapping (1,3). There are no standardized definitions or quantitative measures that exist for diagnostic purposes. For research

purposes, gravimetry is used by collecting sweat on pre-weighed filter paper at different sites of the body, which can be performed for quantitative static analysis (3). Moreover, dynamic quantitative dynamic quantitative sudometry allows the measurement of sweat over time by running dry gas through a measuring chamber and quantifying moisture absorbed from the skin surface (3).

Physiology of thermal regulation

There are approximately 4 million sweat glands in the human body (1). The majority (75%) of these glands are eccrine and are produced during the embryonic stage as no new glands are produced after birth (3). Distribution is uneven, with the highest density in the axillae, palmar and plantar regions (3). Palmar density (700 glands/cm^2) is greater than other areas of the body (4,6).

Eccrine glands are epidermal appendages innervated by cholinergic fibers of the sympathetic nervous system, mainly responsible for thermal regulation by producing sweat, which is both odorless and colorless (1). Sweat is a hypotonic solution in relation to plasma via ductal reabsorption of electrolytes, as it consists mainly of sodium chloride, water, 2-methylphenol, 4-methylphenol, urea and other nitrogen metabolites (1).

Apocrine glands also produce sweat but become active after the onset of puberty via adrenergic nerve fibers (4). Their distribution is localized in axillary and urogenital regions. They do not participate in localized hyperhidrosis, but produce pheromones and other substances, which are converted to odors by bacteria and sebum (3).

Apoeccrine glands are the third type of human sweat glands, found mainly in the adult axillae. It has morphologic and functional features of both apocrine and eccrine glands. It also secretes sweat and is controlled by acetylcholine, which is similar to eccrine glands.

The dissipation of heat is an important aspect of thermal regulation. Mechanisms of regulation involve radiation, conduction, convection and evaporation (3). Evaporation is one of the most effective methods for heat dissipation, as 1L of evaporated liquid is equal to 580 kcal of heat loss from the body (3). The purpose of sweating is to restore the body's normal temperature and maintain the balance between heat input and dissipation (3). It is regulated in the autonomic nervous system via the sympathetic nervous system and its cooling function helps maintain a constant basal temperature. In patients affected with hyperhidrosis, sweating reaction is an abnormal response to heat, stress and exertion and it does not occur in proportion to maintain this homeostasis.

Understanding the sympathetic pathway of the autonomic nervous system is necessary to understand the fundamental relationship between normal thermoregulation and pathophysiology in hyperhidrosis. The efferent sympathetic pathway consists of 3 neurons. The first neuron has its cell body in the hypothalamic sympathetic center (1). Its axon moves downwards by dorsal longitudinal and spinal vestibular fascicles of the spinal cord, then synapsing with the second neuron (1). The second neuron is preganglionic, located in the dorsolateral region of the anterior column of the spinal cord gray matter (7). Pre-ganglionic fibers travel through the white rami communicants, along with the ventral roots of the spinal nerves and head to the paravertebral ganglia of the sympathetic trunk (4). The thoracic sympathetic trunk contains 12 ganglia, located in front of the heads of the ribs posteriorly and covered by a thin layer of parietal pleura (4). The third neuron (postganglionic) leaves the sympathetic chain by gray rami communicants, and joins the spinal nerve, then distributes peripherally to end organ effector cells, including sweat glands. The main neurotransmitter of the neuroglandular junction of postganglionic fibers is acetylcholine, binding to muscarinic receptors in eccrine sweat glands, while noradrenaline is the primary neurotransmitter released between postganglionic nerve terminals and end organ cells in the sympathetic nervous system (7).

Sympathetic cholinergic nerves activate both thermoregulatory and emotional sweating. Stimuli, such as hot environment, physical activity, stress and anxiety, activate the pre-optic area of the hypothalamus, which then releases acetylcholine in neuroglandular junction by sympathetic stimulation (1). This in turn increases the response in the sweat glands, generating a retrograde stimulus to the hypothalamus through the afferent pathways as a negative feedback (1). The balance between the afferent and efferent pathways maintains balance in the body for thermoregulation.

Pathophysiology of hyperhidrosis

The exact pathophysiology of hyperhidrosis remains largely unclear. Most epidemiological studies have shown the existence of a familial trait for primary hyperhidrosis (8,9), as 44% to 66% of patients share a positive family history (10,11). Recent studies have also demonstrated evidence for genetic transmission. A study by Kaufman *et al.* previously showed evidence of genetic autosomal dominant inheritance for primary hyperhidrosis (12). Moreover, an analysis of

the Japanese population presented genetic linkage to foci on chromosome 14q11/2-q13 while another study located foci on chromosome 2q31.1 for focal hyperhidrosis in the Chinese population (13,14). Many studies, however, suggest that this disease is a complex disorder of the autonomic nervous system involving sympathetic and parasympathetic pathways. The most probable explanation is neurogenic over-activity of the reflex circuits innervating the eccrine glands. Increased nervous impulses in the central nervous system can release excessive amounts of acetylcholine, which then increases sudoral response. There is a possibility that normal stimuli can produce an increased nervous tone of the sympathetic fibers that subsequently innervate the sweat glands, leading to exaggerated activity. Exact specifics and nature linking this neurogenic over-activity to primary hyperhidrosis are still unclear.

Interestingly, several studies showed that dysregulation in primary hyperhidrosis is consistent with dysregulation in other autonomic disorders, including sudomotor, baroreceptor and vasomotor disorders (3). Eccrine glands have previously been found to be both histologically and functionally normal in individuals with hyperhidrosis (5), which supports the theory on the dysfunction of the thermoregulation capacity of the sympathetic component of the autonomic nervous system. Moreover, other autonomic disorders have been found to be associated with changes in the regulation of perspiration. In a case study by Diamond *et al.*, the involuntary stimulation of the hypothalamus from removing the brain stimulation probe, used for treatment of essential tremors, led to symptoms of hyperhidrosis (15). Several studies also demonstrated that the reduction in inhibition of the sympathetic system from stroke or trauma led to hyperhidrosis of the contralateral side (16-18). Nonetheless, it is evident that the sympathetic chain at T2 and T3 level is the direct pathway between the hypothalamus and the end organ effector cells, which are the eccrine glands (6). This principle guides the current surgical treatment of hyperhidrosis, which is sympathectomy.

Furthermore, several studies have shown structural and histochemical changes in the sympathetic ganglia, most notably in the size and number of ganglia. Tu *et al.* showed electron micrograph evidence of greater average myelin thickness of the axons in the sympathetic ganglia in patients with primary hyperhidrosis (19). In addition, there may be a component of enzymatic dysregulation in hyperhidrosis. A cross-sectional study using immunohistochemistry by de Moura Júnior *et al.*, which demonstrated an increased expression of acetylcholine and alpha-7 neural nicotinic receptor subunit in the sympathetic ganglia of patients with hyperhidrosis compared to the control group, which supports the theory on hyperactivity of the central portion of the sympathetic nervous system (20). Another study found higher plasma nitric oxide levels in patients with hyperhidrosis in comparison to the control group, which supports another hypothesis that oxidative damage from increased reactive oxygen species production with deficient capacity of antioxidation mechanisms may be involved in the pathogenesis of the disease (21,22).

Specifically, in axillary hyperhidrosis, several studies have shown an abnormal regeneration of sympathetic nerves or an increase in the number or distribution of eccrine glands from hyperstimulation (23). There may also be a component of regulatory dysfunction in addition to the sympathetic hyperactivity (23). Hyperhidrotic glands appeared to be larger than in the control group. In addition, under electron microscopy, these eccrine glands appeared to mainly have features of hyperactivity due to exposure from prolonged stimulation without any structural defects, such as devesiculation of granular cells, distended basal infoldings, canaliculi between non-granular cells, and contracted myoepithelium (23). In contrast, in palmar hyperhidrosis, there was no histopathological finding identified in patients with hyperhidrosis, nor an increase in the number of sweat glands (1).

A recent systematic review on the etiology of primary hyperhidrosis by Hashmonai *et al.* describe three main lines for future research, in order to delineate the pathophysiology of primary hyperhidrosis: genetics, histological observations and enzymatic studies. They outline that the etiology of primary hyperhidrosis may be related to a hereditary genetic trait with pathological alleles in some chromosomes, or histological changes observed in the sympathetic ganglion cells (number, size and thicker myelin sheath) or the higher expression of acetylcholine receptor subunits in the sympathetic ganglia of patients with hyperhidrosis (2).

Conclusions

Primary hyperhidrosis is a neurogenic disorder that is characterized by excessive sweating in certain areas of the body, including axillae and palmar surfaces of hands and feet, resulting from an increased activity of sympathetic cholinergic sudomotor nerves. Pathophysiologic characteristics of primary hyperhidrosis are not well understood, but may be largely caused by the dysfunction of the sympathetic nervous system. Current treatment includes both medical and surgical

therapies, which aim to reduce the impact of the disease on patients' quality of life. Further studies are warranted to clarify the etiology of primary hyperhidrosis, which may aid in the development of improved treatment methods.

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