REVIEW ARTICLE

Hyperhidrosis—Causes and Treatment of Enhanced Sweating

Tanja Schlereth, Marianne Dieterich, Frank Birklein

SUMMARY

Background: Basically two types of sweating exist: thermoregulatory and emotional sweating. They are controlled by different centers: thermo-regulatory sweating is regulated predominantly by the hypothalamus, emotional sweating predominantly by the limbic system. Enhanced sweating, called hyperhidrosis, can be generalized or focal. Primary focal hyperhidrosis is the most common type and affects the axillae, hands, feet, and face—areas principally involved in emotional sweating. Secondary hyperhidrosis develops due to dysfunction of the central or peripheral nervous system.

Methods: Review based on a selective search of the literature via Medline and on the guidelines of the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften [AWMF]).

Results: Various conservative and surgical treatments exist for hyperhidrosis. Conservative treatment options are the local application of aluminum chloride, tap water iontophoresis, and the intracutaneous injection of botulinum toxin. Surgical approaches include endoscopic sympathectomy and axillary tumescent curettage and liposuction, removing the sweat glands. Systemic drugs (e.g. anticholinergic substances) can be used in the treatment of generalized hyperhidrosis.

Conclusion: A step-by-step approach is recommended for the treatment of hyperhidrosis. Local treatment options with few and minor side effects should be tried first.

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Key words: hyperhidrosis, sweating, botulinum toxin, liposuction, surgical treatment

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Sweating is a physiological and vital process. The basic distinction is made between two types of sweating: thermoregulatory and emotional sweating. Most of the sweat glands are of the eccrine type. They produce a thin secretion that is hypotonic to plasma (e1). Eccrine sweat glands are distributed all over the body; their highest density is in the axillary region, on the palms of the hands, and on the soles of the feet (1). Their main function is thermoregulation. Apocrine sweat glands are found primarily in the axillae and the urogenital region. These scent glands become active during puberty and secrete a viscous fluid. They are responsible for a person's "personal," occasionally unpleasant, odor (e1).

Thermoregulation is important to maintain an even body temperature and thus homeostasis (e2). Increased sweating, as in hyperhidrosis, may constitute an important problem. Those affected experience substantial impairments in terms of the social and professional environments because of increased sweat production, and the resultant subjective perception of illness at the individual level may be substantial.

This article explains the neuronal regulation of sweat secretion, aiming to deliver a better understanding of the pathophysiology of hyperhidrosis. We provide an overview of different primary and secondary hyperhidroses, their diagnosis, and therapeutic options.

Methods

This article is based on a selective literature review based on a Medline search and on the guidelines of the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften [AWMF]).

Thermoregulatory sweating

Apart from humans, only few animals—such as apes/monkeys and horses—can evaporate heat through activating eccrine sweat glands (e3). The function of the sweat glands and circulation of the skin is regulated by the sympathetic nervous system. Several feedback loops exist to ensure regulation:

- Most important are thermoregulatory afferences consisting of afferent somatosensory and central thermosensitive neurons.
- The thermoregulatory efferences are sudomotor, vasomotor, and motor efferences.
- The central regulatory center is situated mainly in the hypothalamus (2).

- In the periphery, the amount of secreted sweat is regulated mainly via skin temperature by postganglionic sudomotor fibers innervating sweat glands (e4).

Central mechanisms

An increase in core body temperature—e.g., because of thermogenesis, mostly muscle activity—and skin temperature—e.g., because of sun irradiation—stimulates temperature receptors and thus thermosensory afferences (e2). Receptors of heat and cold are situated in the skin and viscera, which pass impulses via Aδ and C fibers to the central nervous system (2). Central thermosensitive neurons are situated in the spinal cord (e5), the brain stem (reticular formation, raphe nucleus) (e6), and the hypothalamus (preoptic nucleus of the anterior hypothalamus). The hypothalamus is the integration center of all thermosensory afferences (2, 3). Its function is to regulate the body temperature to a level of 37 degrees Celsius (higher if body temperature is raised) (e7). Depending on the degree of agreement of target temperature and actual temperature, thermogenesis—through muscle tremor and cutaneous vasoconstriction—or release of heat—through sweating and cutaneous vasodilatation—is induced (e8).

Numerous other factors of influence—such as hormones, affect, oxygen saturation, plasma osmolarity—also influence thermoregulation and therefore sweating (e2, e9). Progesterone raises the body temperature and lowers the rate of sweating (e10), whereas estrogen has the opposite effect (e11). The sweating rate also falls in case of hypovolemia and a rise in plasma osmolarity (e12); it rises as a result of increased oxygen saturation (e13).

Peripheral mechanisms

The sweat glands are innervated sympathetically by postganglionic fibers (4). The fibers in question are sympathetic C fibers. The released peripheral transmitter is—in contrast to vasomotor efferents—acetylcholine, which binds to postsynaptically localized M3 muscarinic receptors of the eccrine glands and triggers sweat production (e14).

The sweat glands, whose purpose is thermoregulation, are situated all over the entire body surface; the palms of the hands and the soles of the feet have relatively few glands (2). The number of functioning eccrine glands depends on the one hand on intact peripheral innervation (5, e15) and on the other hand on environmental conditions (climate) during early childhood (2). On the periphery, the rate of sweating is regulated by skin temperature and circulation: a rise in skin temperature increases the rate of sweating (e5), cooling down reduces it (e16).

Peripheral and central mechanisms can influence each other mutually. It is thus not surprising that in thermoregulation, there are no linear but complex associations between sweat production on the one hand and body and skin temperature on the other hand (e16). This also partly explains the great variability of sweating between individuals.

Emotional sweating

The second type of sweating is emotional sweating. This serves as a physical "feedback" signal in emotionally affecting sensory, cognitive, and behaviorally relevant processes. Further, it maintains the trophic functions of the sensorily important palms and soles. This type of sweating is regulated by the neocortical and limbic centers (2, 6). The responsible centers are currently not exactly defined, but the amygdala, prefrontal cortex, insular cortex, and cingulum seem to have a major role (e17). The preganglionic and postganglionic (spinal and peripheral) pathways are the same as in thermoregulatory sweating (e2). However—by contrast to thermoregulation, which affects hirsute skin—emotion, stress, or other stimuli mainly stimulate sweat glands in the face, the axillae, the palms, and the soles of the feet (7). Another difference is the simultaneous activation of the vasomotors. Stress induces vasoconstriction, whereas thermoregulatory sweating is accompanied by vasodilatation (e18).

It needs to be borne in mind, however, that the distinction between thermoregulatory and emotional sweating is not an absolute distinction (e19); they have been shown to mutually influence one another (e2). However, the distinction makes the physiology of sweating easier to explain and both types can be examined in a differentiated manner.

Hyperhidrosis

Sweating is a physiological mechanism. However, excessive sweating—hyperhidrosis—can result in substantial individual suffering. Distinction is made between generalized and focal hyperhidrosis (8). Generalized hyperhidrosis affects the entire body and is caused, for example, by

- infections,
- endocrine disturbances and changes (hyperthyroidism, hyperpituitarism, diabetes, menopause and pregnancy, pheochromocytoma, carcinoid syndrome, acromegaly), and
- neurological disorders (e.g., parkinsonism [e20])
- malignancies (myeloproliferative syndromes, Hodgkin's disease),
- medication (e.g., antidepressants),
- intoxication,
- withdrawal of alcohol or other substances (e21).

Primary focal hyperhidrosis develops "idiopathically" in otherwise healthy persons. The onset is mostly in puberty. Altogether, some 3% of the population suffer from hyperhidrosis, 51% of these from focal axillary hyperhidrosis (e22). There does seem to be a genetic predisposition because 30% to 65% of patients have a positive family history (e23). Primary hyperhidrosis affects mainly the axillae (in 79% [e24]), but the feet, hands, and face can also be affected (e21); often, several areas are affected. Changes in sweat gland morphology are not observed. Hyperhidrosis is a complex dysfunction of the sympathetic and parasympathetic nervous system (e25). Patients are often subject to severe psychosocial problems. They often avoid shaking

hands or have unwanted sweat patches under their arms (e1).

Secondary focal hyperhidrosis is the result of central or peripheral neuronal defects. Peripheral causes are neuropathies—e.g., diabetic neuropathy. In this scenario, sweating may be peripherally increased at the onset of a polyneuropathy and may disappear as nerve damage progresses (10, e15). In a scenario of a chronic neurogenic inflammation—such as the complex regional pain syndrome—hyperhidrosis is often found at the extremity that is affected (e26).

After cerebral infarctions or hemorrhages, the failure of cortical inhibitory centers leads to hyperhidrosis contralaterally to the lesion (11). After spinal lesions, sweating is reduced ipsilaterally or may even be completely absent, so that compensatory hyperhidrosis develops on the remaining body parts (e27). Often, patients experience the absence of sweating as less disruptive than the compensatory increase in sweating in other areas. In posttraumatic syringomyelia, hyperhidrosis in the affected area may be one of the first symptoms (12).

Special forms of focal hyperhidrosis include the Harlequin syndrome and Frey's syndrome. In Harlequin syndrome, erythema and hyperhidrosis develop unilaterally. Usually, this is compensatory, increased sweating in contralateral anhidrosis owing to damage to the sympathetic efferences. Harlequin syndrome can be caused by central (brain stem) or peripheral damage to the sympathetic pathways (13). Frey's syndrome—focal gustatory sweating (sweating during eating/drinking, especially of hot foods)—may develop after operations, if tumors are present, or in patients with lesions of the parotid salivary gland with damage to the facial nerve. The result is an aberrant innervation of normally sympathetically innervated facial sweat glands by parasympathetic nerve fibers (chorda tympani) (e28). Gustatory sweating also occurs in families (hereditary gustatory sweating) or as compensatory sweating in patients with diabetes.

Diagnosing sweating disorders

Especially in focal sweating disorders, Minor's starch iodine test is appropriate (13, e29). Iodine solution is applied to the skin and starch powder is applied on top of this. As soon as those substances are in contact with sweat, they assume a violet color. The distribution pattern of the color (or absence of it) often allows conclusions about the cause of the focal sweating disorder (e30).

The amount of sweat can be determined by using quantitative sudometry (5, e31). The amount of sweat released can be measured with a plexiglas capsule and continuous air stream—either the spontaneously released sweat or after stimulation, for example by using iontophoresis of acetylcholine (quantitative sudomotor axon reflex test, QSART) (e15).

To quantify axillary sweating, gravimetry is a particularly suitable test. Filter paper that has been weighed beforehand is inserted into the axilla for a defined time period (60 sec or 5 min) and then weighed again. The difference corresponds to the amount of sweat released in mg/time (15).

BOX

Treatment of hyperhidrosis

Local

- Aluminum chloride 15% to 25% or antiperspirants, L3
- Tap water iontophoresis for palmar/plantar sweating, L2
- Glycopyrrholate for gustatory sweating, L3
- Injections of botulinum toxin, L1

Surgical

- Endoscopic thoracic sympathectomy in sweating disorders of the upper quadrant, L3
- Axillary curettage, liposuction for axillary hyperhidrosis, L4a

Systemic

- Anticholinergic drugs (e.g., methanthelinium bromide), L3
- Tricyclic antidepressants (e.g., amitriptyline), L4a
- Beta blockers, L4a
- Calcium channel blockers (e.g., diltiazem), L4a

L = level of evidence according to the German Agency for Quality in Medicine (Ärztliches Zentrum für Qualität in der Medizin, ÄZQ):

L1: There is sufficient proof of efficacy from systematic reviews (meta-analyses) of many randomized controlled trials

L2: There is proof of efficacy from at least one randomized controlled trial

L3: There is proof of efficacy from methodologically well designed studies without randomization

L4a: There is proof of efficacy from clinical reports

L4b: Represents the opinion of reputable experts, based on clinical experience or reports of expert committees

Unequivocal normative values do not exist; axillary hyperhidrosis is defined as an amount of released sweat of >50 mg/min. On the palm of the hand, values >20 mg/min are considered pathological (e32).

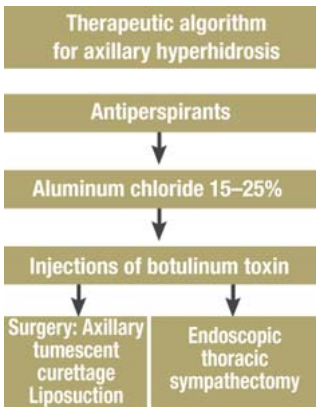
Treatment

Several conservative and surgical options are available to treat hyperhidrosis (*box, figure 1 and figure 2*) (8, 16).

Topical applications

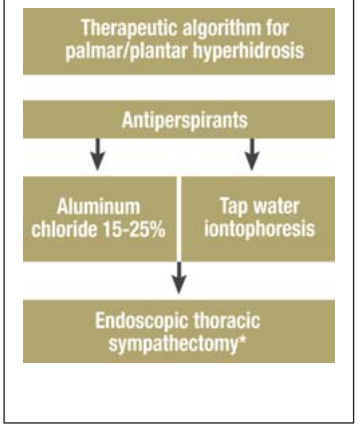
Aluminum salts for topical use are added to many freely available antiperspirants, mostly at concentrations of 1% to 2%. Medications contain aluminum chloride in concentrations of up to 15% to 25%. Repeated daily applications are necessary (e33). Side effects include skin irritations, burning or stabbing dysesthesias. The assumed mechanism of action is the mechanical obstruction of the sweat gland ducts or—after longer term therapy—atrophy of the secretory cells (17). Astringent external substances such as formaldehyde or glutaldehyde are used only to a limited extent as they may cause allergic reactions and local skin irritations (e34). In cases of gustatory sweating (in diabetes or

FIGURE 1



Therapeutic algorithm for axillary hyperhidrosis (adapted from Hornberger J et al.: Recognition, diagnosis, and treatment of primary focal hyperhidrosis. J Am Acad Dermatol 2004; 51: 274–86. [16]; with permission from Elsevier, Oxford)

FIGURE 2



Therapeutic algorithm for palmar/plantar hyperhidrosis. *Only possible in palmar hyperhidrosis (adapted from Hornberger J et al.: Recognition, diagnosis, and treatment of primary focal hyperhidrosis. J Am Acad Dermatol 2004; 51: 274–86. [16]; with permission from Elsevier, Oxford)

Frey's syndrome), 0.5% glycopyrrholate, an anticholinergic substance, may be applied topically (18). Generally, topical applications are suitable only for cases of focal hyperhidrosis.

Tap water iontophoresis is the method of choice for the initial treatment of palmar and plantar hyperhidrosis because of its low side effect profile and effectiveness. The hands or feet are immersed into water or moist electrodes are applied. The standard therapy consists of continuous direct current; alternatively, pulsed direct current can be used, which is easier to handle but probably slightly less effective (19). The assumed mechanism of action is a reversible disruption of the ion transport in the secretory tangle of the sweat glands, possibly owing to accumulation of protons in the sweat gland ducts (e35). This therapy is effective in up to 81% of patients but is very time consuming; initially it should be administered at least three times per week. In the maintenance phase, one session per week should be sufficient. Iontophoresis must not be used in pregnant women or patients with pacemakers. Side effects include erythema, local burning pain, and blistering (20, e36).

Injection of botulinum toxin is the most effective nonsurgical therapy for focal hyperhidrosis *(figure 3)*. Botulinum toxin is a highly effective neurotoxin that is formed by the anaerobic bacterium Clostridium botulinum (15, 21). Botulinum toxin is injected intradermally and inhibits the release of acetylcholine from the sudomotor synapses. The duration of its effect depends on the location and the preparation used and is 4 to 7 months, until the sudomotor nerve fibers have regrown (e37). Initially, botulinum toxin was used to treat muscular dystonias, such as blepharospasm or torticollis. In the meantime, however, it has been licensed for use in axillary hyperhidrosis. The preparations are very costly, however, and several injections are necessary, which may be painful. The main side effect, especially when injected into the hand, is paralysis of the hand muscles (e38). Therapeutic failure owing to antibody formation is possible but extremely rare (8).

Surgical treatment options

In endoscopic thoracic sympathectomy the sympathetic ganglia Th2/3 are removed. Sympathectomy is used especially in palmar hyperhidrosis and leads to long-term improvement in 79% of patients (22, e39). Interestingly, plantar sweating is also reduced when the thoracic sympathetic nerve is severed (in 58% to 85% of patients)—probably because of the absence of the emotional burden of hyperhidrosis on the upper limb. Exact studies into this are lacking, however. The main side effect of this treatment is the development of compensatory hyperhidrosis in body areas that are not supplied by the upper nerve trunk (e40). Surgery-related complications include hemothorax, pneumothorax, Horner's syndrome, injury to the thoracic duct, and damage to the phrenic nerve (e41).

A further surgical therapeutic option in axillary hyperhidrosis is the complete—as far as possible—removal of the axillary sweat glands (e42) by means of axillary curettage (23) or liposuction (24). The success rate of this procedure is 90%, but this is not a trivial procedure. Complications include wound infection, scar formation, skin necrosis, and skin discolorations.

A treatment option for generalized hyperhidrosis is the administration of anticholinergic drugs. Only one randomized, placebo-controlled, double-blind study exists that shows a positive effect of methanthelinium bromide 2×50 mg/d in axillary hyperhidrosis, but not palmar hyperhidrosis. The effectiveness of scopolamine and propantheline has been documented in individual case reports only. Anticholinergic drugs often have side effects such as dry mouth, accommodation disorders, urinary retention, constipation, and memory impairments, which are often therapy limiting factors (25). Antidepressant drugs such as amitriptyline and paroxetine

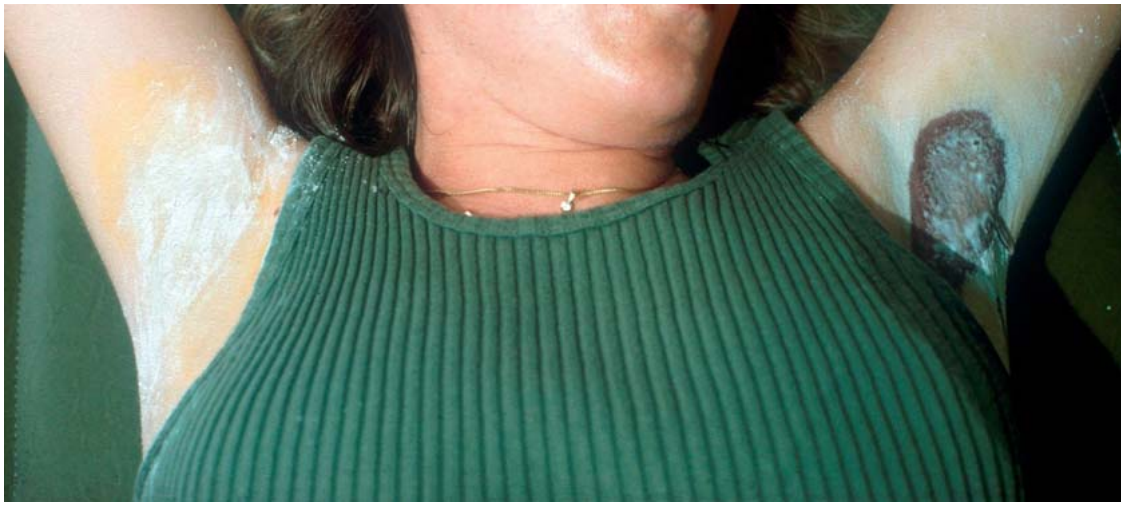


Photo: The photo shows Minor's starch iodine test on both axillae. The right, untreated axilla shows unmistakable hyperhidrosis, indicated by the area stained purple. The left axilla was treated with botulinum toxin and shows no signs of sweating. With permission from Prof. Dr. med. Frank Erbguth, Klinik für Neurologie, Klinikum Nürnberg Süd, Nuremberg (Germany).

(e43), as well as antihypertensive drugs such as beta blockers, calcium channel antagonists (e.g., diltiazem [e44]), alpha antagonists (phentolamine [e45]), and alpha-2 agonists (clonidine [e46]) have been described in single case reports as merely slightly to moderately effective.

Discussion

Several options are available for the treatment of focal and generalized hyperhidrosis; the supporting evidence is of variable quality. For systemic drug treatment of generalized hyperhidrosis, only single case reports exist, but better evidence is available for the treatment of focal hyperhidrosis. According to the guidelines of the German Dermatologic Society (DDG) (8), a stepwise treatment plan is recommended, bearing in mind the location of the problem *(figures 1 and 2)*. All conservative options should be exhausted before surgical therapy is undertaken.

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Conflict of interest statement
Dr Schlereth und Professor Dieterich declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors. Professor Birklein has received honoraria for speaking from Pfizer, Lilly, UCB, Boehringer, and Grünenthal.

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