Psychological Sweating: A Systematic Review Focused on Aetiology and Cutaneous Response

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Key Words
Catecholamines · Emotional sweating · Innervation · Malodour · Stress

Abstract
Psychological sweating in response to emotive stimuli like stress, anxiety and pain occurs over the whole body surface, but is most evident on the palms, soles, face and axilla. This is primarily a consequence of high eccrine sweat gland densities at these body sites. Cholinergic innervation is the primary effector eliciting activation of eccrine sweat glands during periods of acute psychological stress. A dual innervation pathway for eccrine glands (adrenergic and cholinergic) may augment increased sweat output, but this remains to be substantiated. Circulating catecholamines appear not to mediate eccrine gland activity, but may play a role in the activation of apocrine sweat glands. Apocrine sweating is strongly regulated by psychological stimuli and localised to those body sites hosting apocrine glands, with adrenergic peripheral pathways being the primary effector. Accordingly, in the axilla psychological sweating leads to increased sweat output and malodour formation, although this form of sweating at this body site is not observed until puberty.

Introduction
Sweating in response to exercise or high environmental temperature plays an important role in thermoregulation and is effected by eccrine sweat glands. Psychological sweating, also referred to as emotional sweating, in response to emotive stimuli like stress, anxiety, fear and pain occurs over the whole body surface, but is most evident on the palms, soles, face and axilla, and is effected by both apocrine and eccrine sweat glands [1, 2]. Initiation of this form of sweating is not dependent on thermal loading. Apocrine glands exist at birth but do not become active until puberty and, although their specific function is unclear, they are known not to be involved in thermoregulation in humans [3]. Due to the occluded nature and ample supply of eccrine, apocrine sweat and sebum, the human axilla supports a dense cutaneous population of micro-organisms. The metabolic activity associated with this large microbial results in the generation of axillary malodour. Body odours and excessive sweating are perceived as being socially unacceptable conditions known to erode self-confidence and reduce the quality of life. As a consequence many individuals adopt compensatory behaviours to prevent social stigma [4], the most common form of which is the application of an antiperspirant or deodorant.
Table 1. Eccrine sweat gland densities at different body sites (/cm²) cited from different references

<table>
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<tbody>
<tr>
<td>Palms</td>
<td>644</td>
<td>248±92</td>
<td>–</td>
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<tr>
<td>Sole</td>
<td>–</td>
<td>262±98</td>
<td>620±120</td>
</tr>
<tr>
<td>Forehead</td>
<td>–</td>
<td>200±80</td>
<td>360±50</td>
</tr>
<tr>
<td>Forearm</td>
<td>134</td>
<td>112±53</td>
<td>225±25</td>
</tr>
<tr>
<td>Abdomen</td>
<td>127</td>
<td>81±30</td>
<td>190±5</td>
</tr>
<tr>
<td>Upper arm</td>
<td>90</td>
<td>99±42</td>
<td>150±20</td>
</tr>
<tr>
<td>Axilla</td>
<td>68</td>
<td>90±38</td>
<td>130±25</td>
</tr>
<tr>
<td>Thigh</td>
<td>57</td>
<td>125±41</td>
<td>120±10</td>
</tr>
<tr>
<td>Face</td>
<td>59</td>
<td>84±59</td>
<td>320±60</td>
</tr>
<tr>
<td>Back</td>
<td>–</td>
<td>112±32</td>
<td>160±30</td>
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Numerous reviews regarding the structure, function and physiology of both eccrine and apocrine glands are available [5–7]. However, only those aspects of sweat gland biology pertinent to psychological sweating will be included in the current review. As the occurrence of a third type of sweat gland, the ‘apoeccrine’ gland, remains highly controversial, the potential role of these glands in psychological sweating remains to be established and will therefore not be discussed [8].

Sweat Glands – Distribution

Eccrine sweat glands can be found over the whole body surface (1.6–4.0 million) with only a few exceptions: lips, nail bed, nipple, inner preputial surface, labia minora, glans clitoris and glans penis, with the highest sweat gland densities found on the palms and soles (table 1) [9–11]. The human apocrine gland develops from the hair anlagen in the embryo, and is therefore always associated with the hair follicle [12]. Consequently, the majority of apocrine sweat glands can be found in mainly hirsute areas such as the axillae, perineal and areolae regions [7].

Sweat Glands – Innervation and Pharmacology

Eccrine sweat glands are innervated by postganglionic sympathetic fibres of unmyelinated class C type via acetylcholine [5]. However, eccrine sweating can also be stimulated by the intradermal injection of adrenergic agonists [13], and adrenergic neurons have been observed in close proximity to these glands [14]. Nevertheless, physiological sweating, either psychological or thermal, appears to be predominantly cholinergic as it is inhibited by atropine [15]. Denervation of the nerves supporting eccrine glands abolishes gland function completely [16]. This data coupled to the fact that Botox, a potent neurotransmitter antagonist, also severely impairs sweat gland function indicates that a functioning nerve supply is required for normal function [17], and that humoral control of sweating plays little or no role in the primary stimulation of eccrine sweat glands. Although eccrine sweat glands respond to the intradermal injection of catecholamine agonists, quantitatively this adrenergic sweat response represents only 20–50% of that elicited by acetylcholine [18–21]. The reason for a dual sympathetic neural control mechanism is unclear but has been postulated as a mechanism for elevating intracellular cyclic adenosine monophosphate (cAMP) levels in response to adrenergic innervation [22]. The exact function of cAMP in mediating the sweat response is unknown, but is thought to play some role as an intracellular mediator in response to β-adrenergic stimulation [6]. However, there is no evidence to support the theory of adrenergic stimulation amplifying cholinergic sweat production in humans [5]. In addition to control from higher centres, there is evidence that local regional sweating may be stimulated by axon reflex. If acetylcholine is iontophoresed into the skin, sweating is initiated not only in the area surrounding the treated site but also extends radially beyond this point for several centimetres [23, 24].

A variety of other neurotransmitters and humoral agents are known to modulate the secretory function of the eccrine sweat glands. Sweat glands have been shown to be responsive to vasoactive intestinal peptides (VIPs) [25], proteinase-activated receptors (PAR-2) [26], calcitonin gene-related peptide [27], substance P [27], galanin [28] and adenosine triphosphate [29]. PAR-2, adenosine triphosphate and galanin were all shown to increase intracellular Ca²⁺ levels in isolated sweat glands or the eccrine sweat gland cell line NCL-SG3, whereas calcitonin gene-related peptide amplified axon reflex sweating on human skin when administered in combination with acetylcholine. VIPs may have a role in maximizing intracellular cAMP accumulation, together with acetylcholine. In contrast to the other neuropeptides studied, substance P had an inhibitory effect on methacholine-induced sweating [30, 31]. Although eccrine sweat glands respond to a range of pharmacological agents, these play a relatively minor role in modulating gland activity compared to acetylcholine.
The responsiveness of axillary apocrine glands to both adrenergic and cholinergic agents in vivo has been observed [32]. Earlier work indicated that the apocrine secretion is induced only by adrenaline but not by pilocarpine [33]. However, Aoki [32] challenged this view by demonstrating that the milky apocrine sweat can be induced around the hair follicle following intradermal injection of pilocarpine as well as adrenaline. Experiments on isolated axillary apocrine glands demonstrated that the apocrine glands respond to both cholinergic and adrenergic agonists, and that β-adrenergic stimulation is generally more potent than the α-adrenergic counterpart [34]. The responsiveness of the secretory cells to both cholinergic and adrenergic agonists suggests dual activation of apocrine sweat glands. This contention is supported, if not proven, by observations that both catecholamine-containing and cholinesterase-positive nerve fibres surround axillary apocrine glands [14]. The secretory portion of the apocrine gland has been shown to express β2- and β3-adrenoceptors close to the basolateral membrane and purinoceptors in the myoepithelial cells (fig. 1) [3]. These adrenoceptors potentially mediate apocrine sweating in response to stimulation by catecholamines. Contraction of the myoepithelial cells surrounding the glands potentially ‘squeezes’ out the preformed sweat into the follicular infundibulum, this contraction being mediated by adrenergic but not cholinergic agonists [35].

**Psychological Sweating**

Exposure to acute psychological stress initiates immediate physiological and behavioural responses. The so-called fight-or-flight response involves a network of activated mechanisms designed to promote survival in a situation of danger and maintain homeostasis [36, 37]. Psychological stress causes the rapid general discharge of the sympathetic nervous system resulting in the release of catecholamines including adrenaline and noradrenaline, which lead to increases in heart rate, respiration and blood pressure [36]. The hypothalamic-pituitary-adrenocortical (HPA) axis is activated in a slightly slower timeframe, leading to the elevation of circulatory glucocorticoids, including the classical stress hormone, cortisol [37]. Circulating glucocorticoids act at their receptors throughout the body to mobilise stored energy, maintain vasomotor tone, and provide feedback inhibition to further glucocorticoid release [38]. Prolonged stimulation of the HPA axis activates the immune system, leading to mild inflammation [39] through the release of inflammatory mediators including cytokines, free radicals and prostaglandins [38]. Sweating across the whole body, which is most evident on the palm, sole, face and axilla, is also elicited at these times [40]. The same excitatory stimulus (e.g. stressor) can have profoundly different effects on the activation of autonomic, neuroendocrine and immune stress responses between individuals. The level of stressor required to initiate these physiological responses, including sweating, will be dependent on individual responses and is not generic across the population [36].

Sweating on palmar and plantar skin in response to changes in behavioural states has been demonstrated in infants at around 10 days old [41], whereas in the axilla psychological sweating is not initiated until puberty [4]. Psychological sweating is particularly problematic in the axilla due to the occlusive nature of the site, meaning that sweat cannot readily evaporate once formed, so that it accumulates and becomes noticeable both to the individual and others [4, 42]. Concomitant activation of the apocrine glands results in the formation of malodour, which can also be perceived by the self and others in the vicinity [42]. This cascade of sweat secretions and self-perceived awareness of sweat and malodour sets up an escalating and self-sustaining cycle, in which increased anxiety results in more sweating, which in turn leads to more anxiety and so on. Eccrine and apocrine sweat glands in axillary skin can be seen in figure 2.
Central Motor Control of Psychological Sweating

The exact mechanism of the central pathway responsible for psychological sweating is still unclear. Boucsein [43] suggested that electrodermal activity is regulated by the limbic system, motor system (the premotor cortex and basal ganglia) and reticular formation. Thus, it is possible that several brain structures participate in psychological sweating. Although, the amygdala has been proposed to be the key brain centre involved in psychological sweating. The amygdala, which is an important part of the limbic system, is a brain structure critical for memory and is associated with certain psychological conditions, psychological behaviour [44], social behaviour [45] and neuroendocrine and autonomic function [46]. Amygdalotomy in monkeys has been demonstrated to attenuate or abolish electrodermal activity, which reflects psychological sweating in humans [47].

Further studies investigating the functional neuroanatomical system of psychological sweating in humans have also reported that psychological sweating is related to the amygdala. A 19-year-old patient with a past history of herpes simplex encephalitis showed a reduced level of electrodermal responses to mental stress following bilateral amygdalotomy [48]. In patients with bilateral restricted amygdala lesions caused by idiopathic subacute limbic encephalitis, skin electrodermal activity was measured in response to various physical and psychological stimuli, but no sweat stimulation was elicited. After neurological improvement associated with diminution of amygdala lesions, determined by magnetic resonance imaging, normal sweat responses were restored [49, 50]. The direct electrical stimulation of the human amygdala, hippocampus and anterior cingulate gyrus ipsilaterally was reported to elicit electrodermal responses, with the stimulation of the amygdala evoking the most prominent reaction [51]. The origin of psychological sweating using sympathetic skin sweat response (SSSR) was investigated during mental stress tasks in 2 healthy subjects. The results indicated that activation of the frontal cortex, the hippocampus and the amygdala corresponded to an increased SSSR [52].

Localisation of Psychological Sweating

One widely held belief about sweat gland responsiveness is that sweating induced by psychological stimuli is restricted to discrete regions of the body, in particular the glabrous (hairless) skin surfaces (e.g. palms and soles) [53]. However, more compelling data support the notion that emotion-evoked sweating is not limited to particular regions of the body but is a generalised phenomenon, although such sweating (or corresponding electrodermal activity) may only be visible on the palms, soles, axilla and face at normal room temperatures [40, 54–56]. Given the regional differences in sweat gland density outlined previously, it is possible that measurable sweat responses are more readily obtained from the palms, feet and axilla, where sweat glands are more numerous compared to other body sites. In 1 study in which sweat gland density was considered [2], palmar and plantar surfaces exhibited no greater responsiveness to psychological stimuli than did other regions of the body. The investigators instead found emotion-evoked sweat response to be proportional to the number of sweat glands in each region at two different temperatures (26 and 29°C). Given the propensity of glabrous skin surfaces to sweat profusely in response to psychological stimuli, they are relatively unresponsive to moderate exercise, in terms of increased sweat output compared to the majority of body sites [57]. Apocrine sweating is limited to those areas containing apocrine sweat glands, i.e. the axilla and inguinal region, and hence it is only these regions which are responsive to psychological stimuli in the case of apocrine sweat secretion.
Innervation and Pharmacology of Psychological Sweating

The release of catecholamines in response to psychological stimuli has resulted in a general consensus that these hormones are primarily responsible for eliciting the psychological sweating response, particularly at palmar and plantar sites [58, 59]. In addition, others report that some or all of the sympathetic fibres innervating those locations are adrenergic [60–62] or that circulating catecholamines stimulate sweat gland activity directly [63]. Adrenergic fibres are much more sparsely distributed than cholinergic fibres, but have been found in close proximity to sweat glands throughout the skin’s surface (including non-plantar and non-palmar sites) [3]. However, there is ample evidence that adrenergic activation of eccrine sweat glands of local neural origin cannot by itself be responsible for sweating or electrodermal responses [16]. The blockade of local norepinephrine release results in no decrease in skin resistance in response to a variety of psychological stimuli [16]. Atropine, however, blocks all responses under the same conditions [64]. These results suggest that the primary neurotransmitter for mediating (at least part of) the psychological eccrine sweating response is cholinergic in origin [56].

A role for catecholamines in mediating the psychological sweating response at glabrous skin sites cannot be totally ignored. Cutaneous arterioles in glabrous skin are innervated exclusively by noradrenergic sympathetic vasoconstrictor nerves [65–68]. The observation that cutaneous arterioles in plantar and palmar skin are heavily innervated by adrenergic nerves [66–68], which may also innervate adjacent sweat glands [69], leads to the possibility that sweat gland innervation at these regions is influenced by processes mediating cutaneous blood flow in addition to cholinergic stimulation [69, 70]. Such an observation provides a possible mechanism for the increased adrenergic augmentation of sweat gland activity in these regions compared to other body sites, including in response to acute psychological stress. In non-glaborous skin, reflex changes in skin blood flow are mediated by two branches of the sympathetic nervous system (noradrenergic vasoconstrictor nerves and cholinergic active vasodilator nerves) [65, 68, 71]. The exact relationship between sudomotor activity and vasodilation at these sites has yet not been determined. Although it is widely accepted that cholinergic sudomotor nerves innervate sweat glands, whether the sudomotor and vasodilator nerves are one and the same or separate nerves remains to be corroborated [69]. Emerging data supports the belief that efferent signals innervating eccrine sweat glands resulting from both thermal and psychological stresses travel along common neural pathways [40].

Interestingly, limited data exist in support of myoepithelial cells in the secretory portion of the eccrine gland providing a contractile force to facilitate the movement of sweat from the gland lumen to the skin surface [72]. Although the pulsatile nature of eccrine sweat secretion is well established [73, 74], a role for myoepithelial cells in driving this contractile force and the pharmacology mediating the response remain to be determined.

Axillary apocrine sweat glands are known to respond vigorously to emotive stimuli and are physiologically activated by adrenergic and cholinergic agonists [34, 35]. However, myoepithelial contraction of the apocrine glands is purely adrenergic in nature, indicating that the pathway for ‘forcing’ the preformed apocrine sweat out into the follicular infundibulum is mediated via an adrenergic peripheral mechanism [35]. This finding is further supported by the observation that axillary apocrine glands express β2- and β3-adrenoceptors [3]. The available data suggest that apocrine glands respond to psychological stress via a sympathetic peripheral β-adrenergic pathway [3].

Humoral Control of Psychological Sweating

Robertshaw [61] suggested that circulating catecholamines produce effects in two ways: first, by direct local stimulation of eccrine sweat secretion and, second, by indirectly inhibiting secretion by reducing sympathetic outflow to the glands. Evidence for this model is inconclusive. Some early studies reported occasionally observing suppression of sweat under high stress conditions [75]. Later studies reported a more consistent suppression of palmar sweat by epinephrine [76]. Contradictory evidence was reported in patients diagnosed with anxiety neuroses with increased concentrations of circulating catecholamines, who were shown to be more responsive than normal controls to local injections of the cholinomimetic carbachol and phenylephrine [77–79]. However, as the intradermal injection of Botox is highly effective at preventing sweating [80], circulating catecholamines on their own are not capable of eliciting the primary sweat response during periods of acute psychological stress [81], suggesting that the humoral factors play little or no role in the activation of eccrine sweat glands. Sex steroid hormone concentrations have been shown to increase in the initial phase of acute psychosocial stress, though there is
no evidence to suggest that they are directly responsible for the innervation of eccrine or apocrine sweat glands [82]. However, as psychological sweating in the axilla is not apparent before puberty, a role for these hormones in ‘priming’ this site to respond to psychological stress appears likely [83]. Evidence for the humoral control of apocrine glands involving circulating catecholamines remains to be established, but most evidence supports the proposition that human apocrine glands are controlled by the sympathetic nervous system via peripheral mechanisms involving catecholamines [3]. There is no available evidence that the elevation of circulatory glucocorticoids released by the HPA axis in response to psychological stress directly modulates apocrine or eccrine gland activity.

Function

Evolved as a fleeing reaction in different mammals, psychological sweating is thought to be a primitive function that was important when hunting animals or fighting enemies [84]. Physiological amounts of sweat on the palms and soles can improve friction by controlling the humidity of the stratum corneum, leading to an improved grip [85]. The cognitive appraisal of the stressfulness of a particular situation varies between individuals and across gender. Such differences have been observed in many studies in the perception of the stressfulness of a particular situation and the behavioural response to a particular psychological stressor. Stroud et al. [86] reported greater responses in young women to a social rejection challenge than in young men, but larger responses in men to an achievement challenge. Taylor et al. [87] suggested an evolutionary adaptation in females to the predominantly male fight-or-flight response, where the female response might be more accurately referred to as ‘tend and befriend’, such that the female stress response is characterised by caring for offspring and joining social groups to reduce vulnerability [87]. Such results indicate that gender differences exist in the cognitive appraisal to particular stressors, leading to differential triggers of psychological sweating between males and females.

One further consequence of psychological sweating, in particular relating to stress-induced axillary sweat, is the...
release of chemosignals which serve a communicative function in signalling emotional states in human-to-human correspondence [88]. Axillary sweat collected from donors (senders) experiencing a particular stressor reduces perceptual acuity to happy facial expressions [89, 90], whilst the perceptual acuity to negative facial expressions is increased, i.e. fear and anger [91, 92], when presented to receivers under control conditions. Neutral or ambiguous facial expressions increased vigilance in receivers when simultaneously presented with axillary stress-induced sweat [93]. These reactions are not observed when receivers are presented with axillary sweat collected under emotionally neutral control conditions, i.e. non-stressed. These effects have been shown to occur outside conscious awareness and to induce specific neural and behavioural reactions in humans. Therefore, it is postulated that through psychological sweating in the axilla the experience of stress can be chemosensorily transmitted from the sender to the receiver [94].

Conclusions

Psychological sweating in response to emotive stimuli like stress, anxiety, fear and pain can occur over the whole body surface but is most evident on the palms, soles, face and axilla (fig. 3). Cholinergic innervation is the primary effector eliciting activation of the eccrine sweat glands; however, a dual innervation pathway for these glands (adrenergic and cholinergic) may augment some small increase in sweat output during psychological stress events. Although, adrenergic innervation of eccrine sweat glands in the absence of any cholinergic stimulation elicits only a weak response in terms of stimulating gland activity. Circulating catecholamines do not appear to directly mediate eccrine sweat gland activity. Neuropeptides (VIPS) may play a role in psychological sweating in conjunction with cholinergic innervation by augmenting cAMP accumulation in the secretory cells. The level of skin sympathetic nerve activity at different body sites to regulate cutaneous arteriole blood flow may also influence the innervation of adjacent sweat glands, leading to an increased role for adrenergic innervation of sweat glands in these regions. The amygdala appears to be the major brain centre mediating sweat gland activity in response to acute psychological stress. Apocrine sweating is strongly regulated by psychological stimuli and is mediated via an adrenergic peripheral pathway, with secretory activity highly localised to those skin sites hosting apocrine glands. The role of the axilla in psychological sweating, due to the location of both eccrine and apocrine glands resulting in the formation of malodour and visible sweat production, can be problematic; such that acute psychological sweating in the axilla can lead to social embarrassment that can ultimately erode self-confidence and reduce the quality of life.

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