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Neuropeptide PACAP promotes sweat secretion

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Sweat glands are tiny but powerful exocrine glands. In humans, they are spread over the body, and act as a critical mediator for thermoregulation. Sweating action is tightly regulated at several levels of the central nervous system, with thermoregulatory sweating controlled by the hypothalamus.^{1,2} Efferent pulses reach sweat glands through fibres that are sympathetic in origin but acquire cholinergic character via interactions with developing sweat glands. Acetylcholine is the major neurotransmitter, binding to its receptor Chrm3 to activate calcium signalling and NKCC1 cotransporters in secretory cells.^{1–3} The cholinergic route accounts for about 70% of total secretory capacity. The rest was thought to be contributed by α - and β -adrenergic sweating, as suggested by analyses after application of high levels of respective receptor agonists.² However, adrenergic receptors decline sharply in sweat glands upon their acquisition of cholinergic response, and an adrenergic contribution to physiological sweating is thus in some doubt.¹

As an additional candidate complementing cholinergic sweating, the neuropeptide family was implicated for many years.² Neuropeptides comprise a group of small polypeptides that coexist and cotransmit along with major neurotransmitters like acetylcholine or noradrenaline.⁴ The first evidence for a possible involvement was circumstantial: they are found in periglandular nerves, and their receptors are seen in sweat secretory cells. For example, vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP) and galanin were all reported to be expressed in periglandular nerves.^{1,2} However, VIP showed no significant activity in sweat secretion in humans;⁵ CGRP only enhanced acetylcholine-induced sweating;⁵ and galanin knockout and transgenic mice displayed no apparent phenotype.¹ Therefore, the function of neuropeptides in sweat secretion remained conjectural.

In this issue of the *BJD*, Sasaki *et al.*⁶ report the expression of another neuropeptide, the pituitary adenylate cyclase-activating polypeptide (PACAP) – a VIP family member – in periglandular nerves, and also find its receptor, PAC1R, in sweat secretory cells of mice and humans. Furthermore, subcutaneous injection of PACAP induced sweat secretion in mice, which was inhibited by an antagonist of PAC1R.⁶ Thus, the involvement of the PACAP–PAC1R pathway in sweat secretion is demonstrated.

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Conflicts of interest: None to declare.

This study refocuses attention on the role of neuropeptides in sweat secretion, and its features suggest future directions for study. Firstly, the initiation of PACAP-induced sweating was slow and less robust than classic cholinergic sweating. Thus, it remains to be seen if PACAP-mediated sweating truly acts in thermoregulation or may instead modulate it under specific conditions. Secondly, PACAP-induced sweating also appeared distinctive from adrenergic sweating, although the PACAP–PAC1R pathway was known to activate cAMP,⁷ a suggestive second messenger for adrenergic sweating.² PACAP was previously shown to regulate tear secretion, which was largely mediated by aquaporin 5 (AQP5).⁸ But a requirement for AQP5 in sweat secretion is debatable,¹ and any direct connection with PACAP remains unknown. Finally, PAC1R was localized in only a small number of scattered sweat secretory cells – an unexplained feature similar to the limited localization of the Foxa1–Best2 cascade.⁹ Thus, further characterization of PAC1R⁺ secretory cells should provide further evidence of neuropeptide action, and can help to deepen understanding of the regulation of sweat secretion.

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