PERSPECTIVES

How does skin blood flow get so high?

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When humans are exposed to body heating, the large increase in skin blood flow (up to 7–8 l min^{-1}) is of reflex origin and, in non-glabrous skin, most of that is active, distinct from the 'passive' vasodilatation achieved by withdrawal of tonic vasoconstrictor nerve activity (see Johnson *et al.* 1996). This conclusion from classic studies, based on cutaneous nerve block and surgical sympathectomy, has been confirmed through selective pharmacological antagonism of either vasoconstrictor or vasodilator function (Kellogg *et al.* 1991, 1995). Thus, there are at least two independent mechanisms of sympathetic control of the cutaneous circulation: adrenergic vasoconstriction and active vasodilatation (AVD).

How, exactly, AVD works is not clear, nor is there a clear relationship to vasodilator systems in other species. An earlier proposal of a linkage, via the formation of bradykinin, to sudomotor control (Fox & Hilton, 1958), is questioned because bradykinin receptor blockade does not affect AVD (Kellogg *et al.* 2002). The linkage to sweat gland activity remains controversial. Nitric oxide is involved (Kellogg *et al.* 1998; Shastry *et al.* 2000), but the stimulus for its formation is not obvious. There may be a role for acetylcholine. Atropine modestly inhibits AVD while completely inhibiting sweating (Kellogg *et al.* 1995; Shastry *et al.* 2000; Shibasaki *et al.* 2002). Intradermal botulinum toxin A blocks AVD (Kellogg *et al.* 1995). To the extent that it does so through interrupting docking protein function and transmitter release from cholinergic nerves (Humeau *et al.* 2000), one or more sympathetic cholinergic cotransmitters is implied (Kellogg *et al.* 1995).

What is the cotransmitter(s)? Bennett *et al.* (2003) found that a VIP antagonist limited the AVD response to body heating. A limitation to the use of the antagonist stems from its lower affinity for the receptor(s) than that of VIP. To avoid significant background vasodilator effects, antagonist dosages were required that did not completely block the effects of VIP, nor did they completely block AVD, posing the question as to whether the residual AVD was due to VIP or to another substance. As with any of the proposed mediators of AVD, the VIP involvement remains an open question (Wilkins *et al.* 2005).

In this issue of *The Journal of Physiology*, Wong & Minson (2006) raise the provocative notion that Substance P contributes to AVD. They followed the novel tactic of desensitizing NK-1 receptors through exposure to a pulse of exogenous substance P. Another pulse of substance P had a very much reduced vasodilator effect. Importantly, the AVD response to subsequent body heating was similarly reduced, providing evidence favouring Substance P (or NK-1 receptors) involvement. This finding adds to others from the laboratory implicating histamine (Wong *et al.* 2004) and prostaglandins (McCord *et al.* 2006) in AVD. In these cases, traditional antagonists to the putative vasodilators were used. In all cases (Substance P, histamine, prostaglandins, VIP, nitric oxide), intradermal microdialysis was used for drug delivery.

The suggestion that Substance P is a player is also provocative because that vasodilator is considered as coming only from afferent nerves. Does sympathetic AVD somehow engage sensory pathways involved in axon reflexes or do sympathetic vasodilator nerves release substance P? Would an antagonist to NK-1 receptors lead to the same conclusions? Is there another vasodilator transmitter acting on NK-1 receptors? The pathway for the involvement of Substance P, or any other transmitter involved in AVD, must be sensitive to botulinum toxin A and probably includes stimulation of nitric oxide formation. Also, does the use of intradermal microdialysis provide a stimulus for the secretion of some of these vasodilators? Other, equally clever approaches will be required to clarify these issues in order to place all these findings finally into a coherent framework.

These findings by Wong *et al.* (2006) as well as the earlier observations are important steps in unravelling what appears to be a more complex mechanism for AVD than previously thought. If verified, our understanding of cutaneous AVD will undergo significant revision. Rather than a single vasodilator, multiple redundant mechanisms are implicated, much like the evolution of understanding of the metabolic links for vasodilatation in active skeletal muscle. Also similar to active muscle is the difficulty of studying vasodilator function when there are so many players, with probable differences in activation patterns among them. The findings and implications from this very interesting study by Wong *et al* should stimulate that important research.

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