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PERSPECTIVES

How do veins talk to arteries?

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Acute venous congestion of a limb leads to localized vasoconstriction (Skagen, 1983; Henriksen, 1991; Vissing & Secher, 1997). This response exists in all tissues of the limbs, including subcutaneous adipose, muscle and skin. The general nature suggests similar mechanisms. Graded lowering of the limb from above to below heart level has little effect on blood flow until veins are no longer collapsed and venous pressure and volume rise. At that time there is a sharp increase in vascular resistance and a frank reduction in blood flow (Henriksen, 1991). Myogenic mechanisms probably explain the constant flow phase but not the period of significantly reduced blood flow.

The venoarteriolar response is blocked by local anaesthetic (Hassan & Tooke, 1988; Henriksen, 1991). Henriksen (1991) and Crandall *et al.* (2002) showed that vasomotor function was preserved in the presence of local anaesthetic, indicating that local anaesthetic interrupts a neural element, not vascular smooth muscle function, and that venoarteriolar reflex is an appropriate term.

Identification of the nerve types initiating the reflex is not as consistent. In an important series of experiments, Henriksen and colleagues concluded that the response involved activation of sympathetic vasoconstrictor nerves (see Henriksen, 1991). Surgical sympathectomy for hyperhidrosis abolished the venoarteriolar reflex. In an interesting subset, the venoarteriolar reflex was intact one day after sympathectomy, reduced after two days and no longer detectable thereafter, perhaps following the course of nerve degeneration. Also, the venoarteriolar reflex was blocked or markedly reduced by local injections of phentolamine (Henriksen, 1991). The α-adrenergic antagonism of phentolamine implies that the sympathetic vasoconstrictor system is critical for the venoarteriolar reflex, in agreement with the findings following sympathectomy.

Not all previous findings are in accord with the above conclusion, however. Depletion of transmitter from vasoconstrictor terminals in dog hindlimb had no effect on the increased vascular resistance with venous congestion (Folkow & Öberg, 1961). There are examples in which sympathectomy failed to abolish or even reduce the vasomotor response to postural changes of the limb (e.g. Zoltie *et al.* 1989; See Crandall *et al.* 2002). Also, plasma catecholamines rise only marginally when quadriplegic patients are tilted upright (Mathias, *et al.* 1975), a result inconsistent with significant locally initiated sympathoexcitation.

In this issue of *The Journal of Physiology*, Crandall and colleagues (2002) report results from a collection of pharmacological tests of sympathetic involvement in the venoarteriolar reflex. Like others, they demonstrated with lowering of the arm a venoarteriolar reflex in skin that was blocked by topical anaesthetic. However, none of a variety of antiadrenergic drugs had an important effect on the reflex. Presynaptic blockade of sympathetic nerve terminals with intradermal bretylium did not affect the venoarteriolar response, ruling out roles both for noradrenaline and any co-released transmitter (Stephens *et al.* 2001). Delivery of selective antagonists of either α_1 or α_2 adrenoceptors by continuous intracutaneous microdialysis did not influence the venoarteriolar response. Non-specific blockade of α-adrenergic receptors with intradermal phentolamine did not affect the venoarteriolar response. This last point is critical. The key difference from earlier findings is that a much lower concentration of phentolamine (0.1 mg ml^{-1}) was used in the current study than was used previously (10 mg ml^{-1}). The lower dose blocked reflex vasoconstriction, making it unlikely that the discrepancy was due to incomplete adrenergic blockade.

The variety of approaches, the tests of efficacy and the uniformity of implication strongly suggest the sympathetic vasoconstrictor nerves are, in fact, not required for the venoarteriolar reflex. The challenge is to explain this apparent discrepancy. One possibility relates to higher levels of phentolamine having effects beyond antagonism of α-adrenergic receptors. For example, phentolamine antagonizes imidazoline receptors, including ATP-sensitive potassium channels (Edwards & Weston, 1995). Imidazoline receptors are not sensitive to catecholamines. Could it be that these potassium channels, or other imidazoline sensitive sites, are important in the venoarteriolar reflex? This possibility deserves consideration.

If, indeed, sympathetic nerves are not required for the venoarteriolar reflex, why does sympathectomy so frequently blunt or abolish the response? The inconsistency of this result is problematic, but its frequency does not permit its quick dismissal. Possibilities include contributions from spinal or local reflexes with non-adrenergic components. Further, the present study focuses entirely on the cutaneous vasculature. Do the results extend to other regions exhibiting the venoarteriolar reflex? It is important to clarify these issues.

In conclusion, the venoarteriolar reflex is a robust example of local vasomotor control, especially in the extremities. The mechanism for the reflex is not clear but it is important that it is fully understood. The usual implication of sympathetic vasoconstrictor nerves is no longer certain. It is possible that the non-adrenergic effects of phentolamine gave misleading results. Ironically, understanding those effects may lead to clarification of the mechanisms of this local reflex.

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