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COMMENTARY

The fatter the better? Perivascular adipose tissue attenuates vascular contraction through different mechanisms

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Adipose tissue releases several hormones and autacoids and expansion of the adipose tissue and excessive obesity is a risk factor for hypertension. Perivascular adipose tissue, on the other hand, has been reported to lower the vascular tone through the release of a transferable, thermosensitive, non-lipid factor. In this issue of the British Journal of Pharmacology, Gao *et al*. (2007) report that a factor generated by the adipose tissue also stimulates the generation of NO by endothelium and that NO is the predominant mediator of adipose tissue-induced relaxation in endothelium-intact vessels (88 words).
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The incidence of obesity is increasing dramatically in the Western world. Obese subjects have a higher probability of suffering a stroke or a heart attack and present with higher rates of hypertension (Haslam and James, 2005). Adipose tissue itself releases a wide range of different hormones and autacoids into the blood which control the metabolic state and the inflammatory level but also the local blood supply to this highly vascularised organ, by modulating the vascular tone (Trayhurn and Wood, 2005).

Vascular tone itself is affected by a multitude of different mechanisms. Spontaneous myogenic tone and basal tone are modulated either by constriction or vasodilatation by the autonomic nervous system, hormones, local metabolites and autacoids released from adjacent cells such as monocytes and platelets (Pohl *et al*., 2000). In particular, the many different pathways by which the endothelium elicits vasodilator responses have aroused a great deal of interest and it is now known that, besides nitric oxide (NO) and prostacyclin, several other endothelium-derived products gathered under the label 'endothelium-derived hyperpolarizing factor' (EDHF) mediate endothelium-derived vasodilatation (Busse *et al*., 2002).

The importance of other tissues adjacent to the smooth muscle layer in vessels is less well understood. The adventitia has been recognised as a source of reactive-oxygen species (ROS), which limits the bioavailability of endothelium-derived NO. Moreover, NO itself can be produced in the adventitia by the neuronal NO synthase if stimulated appropriately either by local hormones or nerves (Rey and Pagano, 2002).

Recently, several studies have reported that also the perivascular adipose tissue (PVAT) is a modulator of vascular tone and that PVAT lowers the response to a broad spectrum of vasoconstricting agonists by releasing a transferable substance with direct vasodilator properties (Gollasch and Dubrovska, 2004). The chemical nature of this adipocyte-derived relaxing factor (ADRF) is still unclear and, as with EDHF, the mechanism of action as well as the potency of the dilator response varies significantly between species and vascular beds.

In the present issue of the British Journal of Pharmacology, Gao *et al*. (2007) provide important novel information regarding the mechanism of action of ADRF. The authors tested the hypothesis that the ADRF-induced vasodilatation was a consequence of an adipose tissue-mediated stimulation of the endothelium. Indeed, by direct measurements of NO production as well as experiments using NO scavengers and inhibitors of the soluble guanylyl cyclase, they provide evidence that endothelial release of NO is the predominant mechanism mediating ADRF-induced responses in endothelium-intact vascular segments. In fact, the pharmacological profile of ADRF in endothelium-intact segments was totally different from that observed in denuded vascular rings, where ADRF-induced relaxation was sensitive only to tetraethylammonium and the combination of charybdotoxin and apamin. This pharmacological characterization of ARDF in endothelium-denuded segments is in agreement with previous publications reporting that potassium channels are the main effectors of ADRF (Gollasch and Dubrovska, 2004) – although it is certainly somewhat puzzling that, depending on the species and segments studied, different potassium channels appear to be involved in this action and

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that the invasive procedure of endothelial denudation is required to unmask the so far unidentified ADRF.

This, however, is not the only urgent question regarding the physiological importance of ADRF. So far no function of ADRF has been convincingly reported in animals *in vivo*. This is certainly owing to the tremendous technical difficulties associated with 'peeling' off the adventitia from the vessel. Still, the situation *in vivo* may not be totally comparable to what has been carried out in the biotransfer experiments and organ bath studies underlying the discovery of ADRF to date. Will there still be an endothelial component of ADRF if the compound released from the adipose tissue has no direct contact with the endothelium, or if the vessels are continuously flushed with blood? Even more importantly, it is unclear whether there will be any ADRF at all *in vivo* as autacoids present in the highly vascularised adipose tissue are rapidly washed out by the bloodstream. Moreover, blood perfusion *in vivo* will maintain oxygen supply to the adipose tissue, which might be hypoxic in the organ chamber experiments.

The present study as well as previous work consistently reported a role for H_2O_2 as an important vasodilator *ex vivo* (Gil-Longo and Gonzalez-Vazquez, 2005; Gao *et al*., 2007). The contribution of H_2O_2 to vasomotion *in vivo* is, however, less clear. Although H_2O_2 is a vasodilator *in vivo* (Rogers *et al*., 2006), its action is usually observed in situations of low NO bioavailablity or eNOS uncoupling (Suvorava *et al*., 2005). Moreover, some effects, such as the vasodilator response to superoxide dismutase which could be attributed to H_2O_2 generated from superoxide anions, are rather a consequence of an increase in NO bioavailablity (Jung *et al*., 2006). There also exists the notion that *ex vivo* experiments tend to overestimate the contribution of ROS to vasomotor control. Possible reasons for this observation are the excessive oxidative stress generated from the high oxygen tension in Krebs–Henseleit solution in conjunction with the total lack of plasma antioxidants.

With the present study by Gao *et al*. (2007) novel mechanistic information is provided towards our understanding of the vasodilator mechanisms of ADRF. As for the assessment of the physiological relevance of PVAT as a control organ of vascular tone, we are still at the beginning of the project.

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