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Function determines structure in the vasculature: lessons from insulin resistance

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VASCULAR DYSFUNCTION has been well characterized in both human and experimental insulin resistance. Alterations in a range of features of vascular function have been described with insulin resistance (15, 18), including thickened resistance vessel walls with increased structural stiffness (23), reductions in capillary density (rarefaction) (4, 6), reductions in bioavailable nitric oxide (21), increased production of free radicals, augmented vasoconstrictor response to α-adrenergic agonists and to ANG II (3), and augmented production of and responsiveness to endothelin (16, 22, 24). As these features are all present concurrently, it has been difficult to dissect the individual contributions of specific metabolic factors to each component of vascular dysfunction. The broader set of features of the metabolic syndrome also accompany states of insulin resistance, in particular, elevations in blood pressure, further complicating in vivo studies of these relationships. These challenges have made for a body of literature that does not clearly answer the question of which factors are primary in the pathogenesis of vascular dysfunction in insulin resistance.

Endothelial products are widely recognized to contribute to vascular health beyond the acute regulation of vascular function. A timely example of this is the known proatherosclerotic and proinflammatory effects of endothelin, which is mitogenic in addition to exerting acute effects on vascular tone. Nitric oxide has been widely noted to be antiatherosclerotic, but predominantly through antiplatelet effects rather than direct effects on smooth muscle cell proliferation (14). Angiogenesis, however, does appear to depend on the availability of nitric oxide (10). Mice genetically engineered to be deficient in endothelial nitric oxide synthase (eNOS) have a number of hemodynamic and metabolic abnormalities that suggest more than an acute regulatory role of nitric oxide (2, 11, 20), and also exhibit structural abnormalities in blood vessels, including capillary rarefaction (11). The strong association of these structural features with reductions in bioavailable nitric oxide have led to the testable hypothesis that the reductions in nitric oxide bioavailability are directly responsible for these observed structural changes.

In this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Frisbee (4) has rigorously tested this hypothesis. Using a broad set of concurrent measurements of structure and function, studies were performed in leptin receptor-deficient obese Zucker rats (OZR) and their lean counterparts heterozygous for the mutation (LZR). Rats were treated for 4 wk with orally available agents added to their chow. The role of oxidative stress was addressed using Tempol, a superoxide dismutase mimetic, and the role of nitric oxide deficiency was addressed using N⁵,G⁵-nitro-L-arginine methyl ester (L-NAME), a competitive antagonist of nitric oxide synthase. Some rats treated with L-NAME received hydralazine to restore blood pressure, allowing assessment of the independent effects of reduced nitric oxide bioavailability. The expected structural and functional deficits were observed in vessels from OZR, with evidence of increased oxidant stress, impaired basal and stimulated nitric oxide production, reduced microvessel density [histologically determined using a microvessel stain (5)], and altered structural features (reduced passive and active diameter, right-shifted stress/strain relationship, and reduced total distensibility). Antioxidant treatment in these animals with Tempol produced improvements in basal and stimulated nitric oxide production ex vivo and improved stimulated but not basal blood flow in vivo. This was accompanied by an improvement (but not normalization) in microvessel density but without improvement in structural features of resistance vessels. Concurrent treatment with Tempol and L-NAME prevented these improvements, while maintaining the suppression of oxidant stress, suggesting that these effects were attributable to increased nitric oxide bioavailability rather than a nonspecific effect of antioxidant therapy. In LZR, the functional alterations seen in OZR were recapitulated by 4 wk of L-NAME treatment. Although this was not accompanied by alterations in structural features of the vessels, a reduction in microvessel density was seen. These changes persisted when the rise in blood pressure that accompanies L-NAME therapy was prevented by concurrent treatment with hydralazine. In total, these findings argue that the changes in vasodilator function and microvascular density seen in OZR are attributable to impaired nitric oxide bioavailability and that oxidant stress contributes only indirectly via its effects on nitric oxide. The dissociation of these effects from the structural features suggests that other or additional factors are responsible for these changes or that the treatments were of insufficient duration to affect these parameters.

Previously, other investigators have used a similar approach to address the question of the relative roles of nitric oxide bioavailability versus hypertension in the pathogenesis of microvascular rarefaction. In one report, the effect of NOS inhibition to induce rarefaction was partially reversible with spironolactone, enalapril, and verapamil (17). These findings suggested that the relevant effect was the induction of hypertension rather than a specific antagonism of NOS, but this study was less rigorous than the current paper by Frisbee in demonstrating whether the antihypertensive therapy used, in fact, altered the suppression of nitric oxide. In direct contrast to the current study, eNOS-deficient mice developed microvas-
cular rarefaction concurrently with hypertension as they aged, and this phenomenon was prevented by concurrent hydralazine treatment (11). Thus, although the current findings by Frisbee are internally consistent, there is some conflict with studies from other authors regarding the relative contributions of hypertension per se versus nitric oxide deficiency in the loss of microvascular networks.

In humans, the association of reduced capillary density with insulin resistance has been repeatedly demonstrated (8, 9, 13, 19). Further, an association of capillary density with impairments in insulin-induced vasodilation in elderly men has been reported (7), which more directly ties insulin’s nitric oxide-dependent vascular actions (25) to these structural changes. However, much remains to be done to better understand these interrelationships, specifically regarding the question of how therapies addressing vascular function or insulin sensitivity might alter these parameters, and what impact this might have on skeletal muscle function and metabolism.

Does capillary rarefaction contribute to hypertension or insulin resistance independently of impairments in nitric oxide bioavailability? Mice deficient in eNOS have increased vascular resistance and capillary rarefaction, with separate contributions of each of these features to elevated blood pressure (12). We know that insulin signals through typical insulin receptor signaling pathways to eNOS (25) and that this action is impaired in parallel with impaired metabolic actions of insulin in states of insulin resistance. Observations that eNOS-deficient mice recapitulate not just insulin resistance but also other systemic features of insulin resistance (2, 20) suggest that this action of insulin is a key component of overall insulin action. In humans, coinfusion of $N^\omega$-monomethyl-L-arginine with insulin acutely reduces insulin’s metabolic effects (1), on a timescale that is too short to involve structural changes. These observations suggest that vascular function (reflected in nitric oxide bioavailability) contributes importantly to overall insulin action. However, relatively little has been done in humans or in animal models of insulin resistance to explore the independent contributions of vascular dysfunction and structural alterations to metabolic status.

The present paper suggests that nitric oxide bioavailability drives microvascular structure and that the adverse changes with insulin resistance can be reversed through therapy to reduce nitric oxide consumption by superoxide. More generally, this provides hope that the structural, as well as functional vascular abnormalities in insulin resistance, can be improved with therapies targeting the vasculature. These findings will ultimately be reflected in the treatment of hypertension, as well as the treatment of insulin-resistant states like the metabolic syndrome.

REFERENCES


