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COMMENTARY

Anti-hypertensive therapy and insulin sensitivity: regulation through the microcirculation?

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Type 2 diabetes mellitus is one of the most common and costly diseases facing society. It is often accompanied by hypertension, whether antecedent or following the development of Type 2 diabetes. Therapies to treat hypertension have the potential to affect insulin sensitivity in peripheral tissues, potentially worsening or ameliorating glucose homeostasis and Type 2 diabetes. On one hand, pharmacological agents such as thiazide diuretics may act to reduce insulin sensitivity. Conversely, agents such as angiotensin II type 1 (AT1) receptor antagonists have the potential to enhance insulin sensitivity, although some studies show equivocal results.[1] The investigation of the use of concurrent pharmacological therapy to offset potentially negative effects on insulin sensitivity has been limited and, furthermore, the literature is lacking in reports of putative mechanisms by which these therapies may be acting and interacting with each another.

In this edition of *Hypertension Research*, Guo *et al.*[2] report the results of their study testing the hypothesis that losartan can prevent the hydrochlorothiazide (HCTZ)-induced reduction in insulin sensitivity through modulation of skeletal muscle capillarization in a fructose-fed rat (FFR) model. The study design permitted the authors to assess the effect-modifying roles of diet and pharmacological agents on insulin sensitivity and skeletal muscle capillarization in hypertension. The study is unique in that it takes a diet-induced model of hypertension and metabolic syndrome, and looks at the independent and interactive effects of two common anti-hypertensive medications on insulin sensitivity, with further exploration of mechanisms by which the drugs may mediate insulin sensitivity. The authors chose a FFR model of systolic hypertension that also exhibits insulin resistance; it is proposed that a common link to both of these is vascular dysfunction.[3] FFR exhibit vascular dysfunction in the form of reduced endothelium-dependent vasodilation and capillary rarefaction, factors that may be affected by HCTZ and losartan (see Figure 1). In the present report, Guo *et al.*[2] focused on the effect of HCTZ and losartan on the skeletal muscle capillarization and subsequent insulin sensitivity. The authors report that in FFR without pharmacological therapy, there was reduced capillary density and insulin-stimulated glucose uptake, and that treatment with HCTZ exacerbated the reduction in both the measures. Interestingly, treatment with losartan restored capillary density and glucose uptake to near-control levels, when given independently and in tandem with HCTZ.

Support for a role of skeletal muscle capillarization in partially determining insulin sensitivity comes in several forms. In humans, studies show direct correlations between measures of skeletal muscle capillarization and measures of insulin sensitivity.[4–6] Skeletal muscle is the major site of insulin-stimulated glucose uptake, and a reduction in skeletal muscle capillarization has the net effect of increasing the diffusion distance of insulin and glucose from capillaries to skeletal muscle, thereby reducing glucose uptake. Inhibition of the renin–angiotensin system by AT1 receptor antagonists such as losartan has the potential to increase insulin sensitivity in part by increasing muscle blood flow, but less attention has been given to the effects on the microcirculation and skeletal muscle capillarization. Although blood flow indeed increases muscle perfusion, studies in rodents show that insulin-mediated glucose uptake in skeletal muscle[7] can be altered by limiting the number of capillaries perfused, independent of blood flow. These studies support a direct and independent contribution of capillarization to insulin sensitivity.

Human and animal studies have explored the effect of losartan on measures of insulin resistance and sensitivity, but the study of the mechanisms underlying the effects of losartan has largely been limited to the measurement

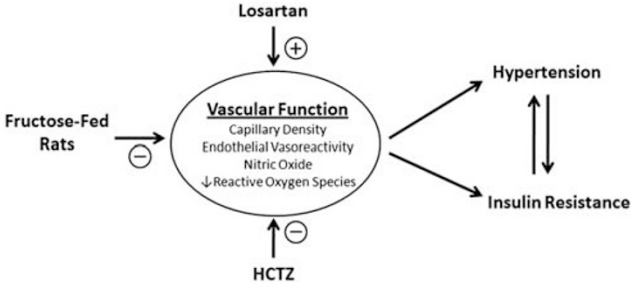

Figure 1 Potential modulation of hypertension and insulin resistance through the vasculature by HCTZ and losartan.

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of circulating biomarkers, and not on factors within skeletal muscle or other tissue depots. In particular, skeletal muscle capillarization has not been investigated as a mechanism by which losartan may increase insulin sensitivity. Likewise, many previous studies have used less sensitive estimates of insulin sensitivity and approaches that were less mechanistic in nature than the present report. Here, the authors use the 'gold standard' hyperinsulinemic-euglycemic clamp to measure insulin-stimulated glucose uptake and harvested extensor digitorum longus (EDL) muscle for the measurement of skeletal muscle capillarization. In the present report, HCTZ was found to reduce capillarization in EDL from FFR, and losartan was found to increase skeletal muscle capillarization in EDL from FFR whether independent or in conjunction with HCTZ.[2] Multivariate regression analysis confirmed a correlation of capillary density with insulin-stimulated glucose uptake, independent of changes in body weight, blood pressure, adiponectin and triglycerides. Although this does not establish cause and effect, the fact that capillary density explained up to one-third of the variation in insulin-stimulated glucose uptake regardless of the intervention and other mitigating factors is corroboratory, especially considering direct evidence from the other rodent models. Still, it must be noted that although this analysis indicates a role of capillarization in insulin sensitivity, the authors assessed a limited number of factors and could not assess others that may contribute to glucose uptake in skeletal muscle (for example, glucose transporter-4 or inflammatory markers).

In their study, the authors chose to use EDL, a muscle rich in type II fibers, as opposed to soleus muscle, which has a high proportion of type I fibers. At first, this may seem counter-intuitive as higher insulin-stimulated glucose uptake is associated with a higher type I fiber proportion in skeletal muscle;[8] however, this viewpoint may only take into account the metabolic properties of muscle fibers themselves. Although differences in insulin sensitivity among individual fiber types may be due to intracellular metabolic differences, they may also be in part due to the extracellular environment in muscle. Type II fibers typically have lower capillarization compared with type I; therefore, a shift in fiber type or in fiber-type-specific capillarization in fibers may affect insulin sensitivity. Whether the reduction (HCTZ mediated) or increase (losartan mediated) observed in EDL is truly fiber type specific, or whether there are overall changes in capillarization across fiber types will need to be elucidated (for example, determining whether FFR, HCTZ and losartan have similar effects on capillarization in soleus muscle). Our group has studied fiber-type-specific capillarization in human stroke subjects, where muscle from the paretic limb has a much higher proportion of type II fibers compared with controls.[6] Although there is a higher rate of insulin resistance in these subjects, trends in the relationship with capillary density were similar across fiber types indicating that overall capillary density, not specific to on fiber type, was associated with worse glucose tolerance.[6] Given these findings, as well as the potential mechanisms by which losartan may affect capillarization, it seems possible that the effect of losartan may not be fiber type specific.

The authors propose three mechanisms by which losartan may increase skeletal muscle capillarization: (1) the direct hypotensive effect of losartan, (2) an increase in angiogenic growth factor expression and (3) increased progenitor cell function. Although these were not directly measured in the present report, these mechanisms are supported by previous studies. Skeletal muscle capillarization is reduced in hypertension;[9] therefore, if a normotensive environment is restored, one might expect a return to higher levels of capillarization. However, if the increase in capillarization was solely due to reduced blood pressure, HCTZ given as an anti-hypertensive agent would not be expected to reduce capillarization. Losartan may affect capillarization by promoting a pro-angiogenic environment. For example, skeletal muscle vascular endothelial growth factor (VEGF—a potent angiogenic growth factor) protein levels are lower in hypertensive subjects,[9] and losartan, by blocking the AT1 receptor, may enhance angiotensin II signaling through the angiotensin II type 2 (AT2) receptor to increase VEGF expression.[10] Also, there is evidence from rodent models that losartan may increase circulating progenitor cell function.[11,12] Losartan prevents the decrease in endothelial progenitor cells observed in a nephrectomized rat model,[11] and may do the same in hypertension and insulin resistance, where circulating EPC number is reduced. This is possibly mediated through an increase in VEGF levels[11] and decrease in reactive oxygen species.[12] Elevated levels of reactive oxygen species may be linked to the mitochondrial dysfunction common to both insulin resistance and vascular dysfunction. We and others have shown that increased NADPH oxidase activity and increased mitochondrial-derived reactive oxygen species in putative endothelial progenitor cells from the humans may be detrimental to their function.[13,14] To date, the mechanisms underlying any effect of anti-hypertensive agents on capillarization is speculative, and it will be important for future studies to examine these mechanisms in detail to optimize therapeutic benefit.

Regardless of the precise mechanism of action, the findings that the AT1 receptor antagonist losartan reverses HCTZ-exacerbated insulin resistance and that this may be mediated by increasing skeletal muscle capillary density have potentially significant clinical implications. Given that the present findings are in a rodent model, they cannot automatically be extrapolated to the humans. An important next step will be to extend these studies to human subjects—first determining whether thiazide diuretics contribute to reduced skeletal muscle capillarization and insulin sensitivity, and then determining whether losartan therapy concurrent with HCTZ may prevent the negative effect of HCTZ on insulin sensitivity. This has the potential to impact therapeutic recommendations in hypertensive patients, especially those for whom thiazide diuretic therapy is initiated.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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