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Uncovering a Mineralocorticoid Receptor–Dependent Adipose–Vascular Axis: Implications for Vascular Dysfunction in Obesity?



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Obesity, insulin resistance, and type 2 diabetes mellitus (T2DM) are associated with increased levels of aldosterone and activation of cardiovascular mineralocorticoid receptors (MRs) contributing to hypertension and associated cardiovascular disease (CVD) (1). Large randomized controlled trials such as the Randomized Aldactone Evaluation Study (RALES), the Epleroneone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), and the Epleroneone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) have demonstrated the CVD-related mortality and morbidity benefits of MR antagonists, further implicating MR signaling as a key mediator of CVD (2). The actions of kidney MR signaling to increase cardiovascular and renal fibrosis and blood pressure is well known; however, recent research suggests that inappropriate activation of extrarenal MR signaling in vascular endothelial cells (ECs), vascular smooth muscle cells (VSMCs), immune cells, and adipocytes promotes insulin resistance, T2DM, and associated CVD (1,3,4). For example, in association with obesity and insulin resistance, perivascular and visceral adipose tissue (PVAT and VAT) is dysfunctional, in part, because of adipose MR activation (3). Furthermore, PVAT and VAT secrete aldosterone, the ligand for MRs in endothelial and smooth muscle cells, and this is increased in obesity (3,4).

PVAT is a unique depot of adipose tissue that surrounds blood vessels to provide mechanical protection and helps regulate blood vessel tone (5,6). PVAT exerts divergent effects in different vascular beds, perhaps related to differences in fat constitution (5,6). For example, the thoracic aorta is surrounded by brown adipose tissue (BAT) and

white adipose tissue (WAT), whereas the abdominal aorta is surrounded only by WAT (6). In rodents, the mesenteric artery is enmeshed in WAT, which is traditionally expanded in conditions of obesity and insulin resistance. Under normal physiological conditions, PVAT releases vasodilator substances such as adiponectin and adipocyte-derived relaxing factors that contribute to the maintenance of normal vascular tone (5,6). In pathological conditions such as obesity, however, enhanced MR signaling in PVAT and VAT activates NADPH oxidase–derived reactive oxygen species and releases proinflammatory adipokines such as visfatin, resistin, tumor necrosis factor- α , and interleukin-6, contributing to impaired vascular insulin metabolic signaling and vascular relaxation (3,7). Indeed, in the Framingham Heart Study (FHS), increased PVAT was an independent risk factor for CVD (8). The effect of PVAT to modulate vasodilation in health and disease is well established; however, much less is known about the impact of MR-dependent adipose signaling on vascular constriction. One recent study demonstrated that coronary PVAT from obese swine augments coronary contractile responsiveness (9).

In this issue of *Diabetes*, Nguyen Dinh Cat et al. (10) address this issue by evaluating the role of adipocyte-specific MR overexpression, previously shown to promote obesity and insulin resistance, in the regulation of mesenteric microvascular contractility. Increased adipocyte MR activation promoted an increase in adipose-derived hydrogen peroxide (H₂O₂), a vasodilatory reactive oxygen species, and impaired arteriolar vascular smooth muscle contractility involving upregulation of vascular redox–sensitive protein kinase G (PKG)-1, downregulation of redox-sensitive Rho kinase (ROCK) activity, and increased elastin content.

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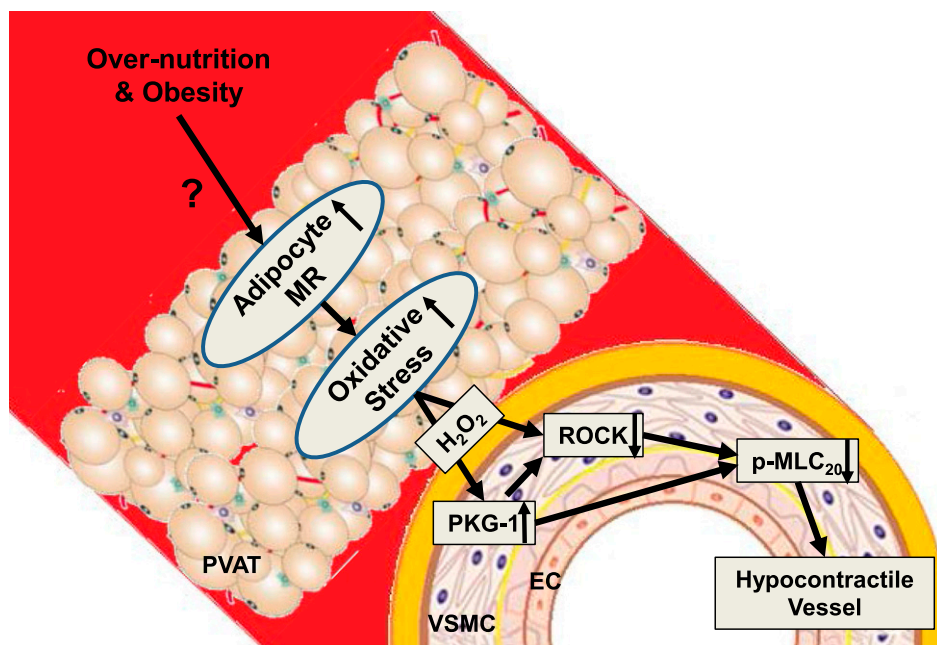


Figure 1—Mechanisms of adipocyte MR overexpression-dependent signaling in the modulation of mesenteric vascular contractility. p-MLC₂₀, phosphorylation of MLC.

The changes in PKG-1 and ROCK converge to decrease myosin light chain (MLC) kinase phosphorylation/activation, MLC phosphorylation, and calcium sensitivity of smooth muscle contractile machinery (Fig. 1). Thus, overexpression of adipocyte MR leads to production of adipocyte-derived H₂O₂ and an intriguing vascular phenotype providing insight into the complexity of adipose-vascular interactions in conditions of increased MR signaling such as obesity.

Overall, these new and interesting data emphasize the functional importance of adipocyte MR in CVD complications associated with obesity. Indeed, adipose MR overexpression resulted in increased adiposity owing to the known adipogenic actions of MR signaling (7). Therefore, this model presents a unique phenotype of MR-dependent adipose expansion resulting in a unique hypocontractile vascular phenotype that contrasts that typically seen in obesity models such as diet-induced obesity. For example, over-nutrition and insulin resistance usually increase vascular contractility, in part, via enhanced ROCK activity, impaired insulin metabolic signaling, reduced nitric oxide bioavailability, and decreased PKG/cyclic guanosine monophosphate in resistance vessels (1,3). These divergent results are consistent with data revealing impaired vasodilation but not adipose inflammation/dysfunction following aldosterone infusion in rodents (11,12). Thus, in the context of available evidence, this study highlights an MR-dependent adipose-vascular axis that may modulate MR-dependent effects in other tissues (i.e., ECs and VSMCs) in states associated with more “global” MR overactivation. Of additional interest is the finding that adipose MR overexpression was associated with increased arteriolar elastin content and reduced

vascular stiffness. On the surface this may appear inconsistent with available evidence of profibrotic MR signaling and increased vascular stiffening in models of obesity. The impact of obesity and MR signaling on microvascular versus macrovascular stiffening, however, remains unclear as divergent structural remodeling within and among resistance and conduit vessels has been described in obesity (13–16) consistent with the current study.

In conclusion, data in the current study (10) presents an exciting paradigm of relevant functional cross talk between adipocyte MR and vascular contractility and remodeling in mesenteric resistance vessels. This study highlights the intricacies of tissue-specific MR signaling and the dramatic interactions of MR signaling across tissues as contributors to CVD-associated impairments of vascular function and blood flow control. Further studies are warranted to more definitively define the role of adipocyte-specific MR and PVAT in other adipose and vascular beds, particularly in conditions of obesity and insulin resistance.

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