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clear AKI-induced distant organ toxins? Earlier initiation of dialysis? Continuous dialysis over intermittent? Improved membranes? Novel dialysis approaches, such as the renal assist device? Pharmacologic approaches to block deleterious pathways induced by AKI? A major opportunity clearly exists to improve our care of AKI patients, and studies on complex inter-organ cross talk will guide rational interventions in this common, often catastrophic, syndrome.

DISCLOSURE

The authors declared no competing interests.

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Renin–angiotensin system blockade and diabetes: moving the adipose organ from the periphery to the center

Oliver Lenz[1] and Alessia Fornoni[1,2]

Lee *et al.* report that an angiotensin II type 1 receptor blocker (ARB) improved glucose intolerance in OLETF rats, an experimental model of type 2 diabetes. ARB treatment resulted in modulation of the adipose tissue, leading to an increased number of small, differentiated adipocytes able to produce more adiponectin and less monocyte chemoattractant protein-1 and plasminogen activator inhibitor-1. This supports the relevance of the functional interplay between adipose tissue and the renin–angiotensin system in states of insulin resistance.

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A large body of literature suggests that renin–angiotensin system (RAS) blockade with either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker (ARB) will prevent new-onset type 2 diabetes.[1] Two receptors for angiotensin II have been described in humans, the angiotensin II type 1 (AT1) and type 2 (AT2) receptors. Among them, the AT1 receptor seems to be primarily responsible for the metabolic effect of RAS blockade.[2] In fact, the AT1 and AT2 receptors may have antagonistic activities on glucose uptake and cell differentiation in adipose tissue, as suggested by studies performed in AT2-null mice.[3] How RAS blockade leads to a diminished incidence of type 2 diabetes remains to be fully elucidated. The following mechanisms are being investigated (Figure 1): upregulation of muscle glucose uptake via modulation of glucose transporter-4 (GLUT4) and blood flow;[4] improvement of pancreatic β-cell function;[5] modulation of hormonal responses from adipose tissue;[2] decreased hepatic gluconeogenesis and increased free fatty acid oxidation;[6] improvement of endothelial function through down-regulation of NADPH oxidase;[2] direct stimulation of insulin signaling at multiple levels;[7] and direct regulation of peroxisome proliferator-activated receptor-γ (PPARγ) by selected ARBs, such as telmisartan and irbesartan.[8] Experimental data suggest that RAS-blocking agents that act on more than one pathway might be more effective for the prevention of

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diabetes. However, a large clinical trial failed to show an advantage of telmisartan over ramipril, suggesting that the inherent agonistic action of telmisartan on PPARγ may have less clinical relevance than initially hypothesized.[9]

Recent investigations have focused on the cross-talk between adipose tissue and organs affected by macrovascular and microvascular complications of diabetes. Among the various cytokine-like hormones secreted by adipose tissue, also referred to as adipokines, adiponectin is the most abundant.[10] Adiponectin expression inversely correlates with the development of insulin resistance and cardiovascular disease, and a polymorphism in the adiponectin promoter affecting gene expression has been linked to diabetes and its complications.[11] Adiponectin-null mice develop severe proteinuria and podocyte damage, which can be reversed by the administration of recombinant adiponectin, establishing a cause–effect relation between adiponectin and albuminuria, a marker of both insulin resistance and early diabetic nephropathy.[12] Whether a similar mechanism may be at play in patients with diabetic nephropathy remains to be seen. It is possible that modulation of adiponectin production by RAS blockade may provide a unifying explanation for the metabolic, cardiovascular, and renal protection afforded by angiotensin-converting enzyme inhibitors and ARBs.

The work of Lee et al.[13] (this issue) provides experimental evidence that treatment with an ARB (L158809) is associated with a blood pressure–independent increase in small differentiated adipocytes and increased adiponectin concentrations in the adipose tissue of a rat model of diabetes, the OLETF rat, consistent with a recent report in KK-Ay mice.[2] Angiotensin II-induced oxidative stress and upregulation of plasminogen activator inhibitor-1, monocyte chemoattractant protein-1, and nuclear factor-κB expression could be improved *in vitro* by treatment with an ARB, which coincided with increased adiponectin and PPARγ expression. The lack of changes in insulin and C-peptide concentration and insulin-resistive indices after ARB administration suggests that modulation of adipokines or GLUT4 function represents the most likely mechanism by which ARBs improve glycemia in the described model.

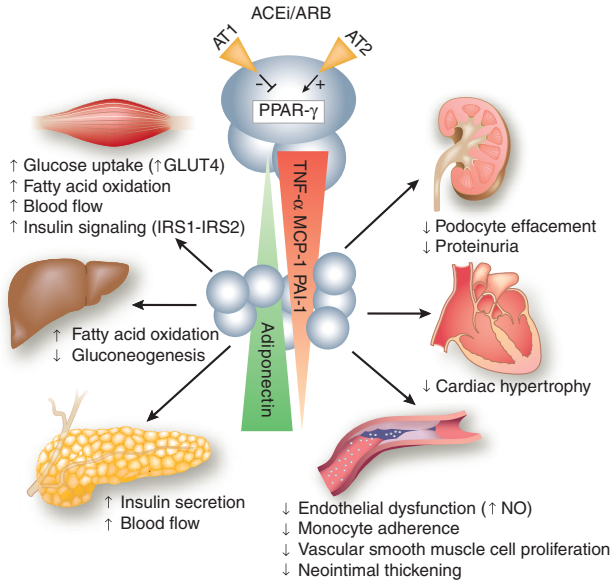

Figure 1 | Key functions of adipocytes in the pathogenesis of insulin resistance. Large dedifferentiated adipocytes characterize insulin-resistant states. Blockade of the renin–angiotensin system via either an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) restores small, differentiated adipocytes via angiotensin II type 1 (AT1), AT2, and peroxisome proliferator-activated receptor-γ (PPARγ) receptors. Small, differentiated adipocytes produce less tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), and plasminogen activator inhibitor-1 (PAI-1), and more adiponectin. Adiponectin affects glucose uptake and metabolism in skeletal muscle and liver, pancreatic β-cell function, endothelial function, and development of albuminuria. GLUT4, glucose transporter-4; IRS, insulin receptor substrate; NO, nitric oxide.

Diabetes and its complications are associated with a chronic inflammatory state that directly correlates with the degree of insulin resistance and endothelial dysfunction. In contrast, adiponectin inversely correlates with insulin resistance and has a wide range of anti-inflammatory properties.[10] In macrophages, adiponectin reduces the transformation of macrophages to foam cells and suppresses the class A scavenger receptor; it reduces lipopolysaccharide-induced tumor necrosis factor-α expression; it reduces nuclear factor-κB activation; and it affects the expression of adhesion molecules responsible for monocyte adhesion to endothelial cells. In addition, adiponectin reduces the lipopolysaccharide-induced expression of several chemokines without affecting their corresponding receptor CXCR3 in macrophages. At the same time, adiponectin does not suppress chemokine induction by interferon-γ; this supports the notion that adiponectin works via the Toll-like receptor-4 (TLR4) signaling pathway. This is very interesting, as TLR4 has been implicated in the development of atherosclerosis, insulin resistance, and proteinuria. A more detailed characterization of the interaction among the hormonal response of the adipose organ in diabetes, adaptive immunity, and development of insulin resistance may shed light on novel mechanisms responsible for the development of diabetes. Further studies are needed to determine to what extent the anti-inflammatory effects of RAS blockade and adiponectin share common pathways. The impact of such anti-inflammatory actions on the development of type 2 diabetes also requires additional analysis, as a randomized clinical trial in a prediabetic population failed to show a benefit of ramipril over placebo to prevent new-onset type 2 diabetes.[14] Additional insight may be gained by investigating downstream therapeutic targets, such as adiponectin *per se*, rather than focusing on the effect of widely used medications on the hormonal function of adipose tissue. In particular, a more

detailed characterization of the pattern of distribution of adiponectin receptors 1 and 2 is needed, as adiponectin receptors have been fully characterized solely in muscle, liver, kidney, and macrophages. Once the tissue distribution of adiponectin receptors is known, the development of specific adiponectin receptor modulators that can be orally administered and have a longer half-life than adiponectin may represent a novel treatment strategy for the prevention or cure of type 2 diabetes and its complications.

DISCLOSURE

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