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Microvascular Dysfunction in Obesity: A Potential Mechanism in the Pathogenesis of Obesity-Associated Insulin Resistance and Hypertension

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Obesity is an important risk factor for insulin resistance and hypertension and plays a central role in the metabolic syndrome. Insight into the pathophysiology of this syndrome may lead to new treatments. This paper has reviewed the evidence for an important role for the microcirculation as a possible link between obesity, insulin resistance and hypertension.

The clustering of cardiovascular risk factors, including obesity and central fat distribution, hypertension, insulin resistance, dyslipidaemia, and proinflammatory and prothrombotic factors, has been recognized for many years and is often referred to as the metabolic syndrome (1, 47). Abdominal obesity is considered to play a central role in this syndrome and is a major risk factor for chronic diseases such as Type 2 diabetes mellitus and cardiovascular disease (49, 88). The incidence of obesity is progressively increasing worldwide and has reached epidemic proportions in several countries (37). Consequently, the prevalence of obesity-related disorders, such as insulin resistance and hypertension, is also increasing at an alarming rate. Although this is well recognized, the underlying mechanisms of obesity and obesity-related disorders remain relatively poorly understood. Unraveling these mechanisms is very important because it may lead to the development of therapeutic strategies that target the development of obesity-associated clinical disorders and, eventually, the development of Type 2 diabetes mellitus and cardiovascular disease.

Microvascular dysfunction may affect both peripheral vascular resistance (5, 75) and insulin-mediated glucose disposal (19, 92, 94, 117), thereby contributing to hypertension and insulin resistance, respectively. Recently, it has become clear that obesity is characterized by microvascular alterations (3, 29, 94). Therefore, we suggest that obesity may be a primary cause of microvascular dysfunction resulting in changes in pressure and flow patterns and, consequently, obesity-related hypertension and insulin resistance.

Microcirculation (Definition and Functions)

The microcirculation is widely taken to encompass vessels <150 μm in diameter. It therefore includes arterioles, capillaries, and venules. Nowadays, a definition based on arterial vessel physiology rather than diameter or structure has been proposed, depending on the response of the isolated vessel to increased internal pressure. By this definition, all vessels that respond to increasing pressure by a myogenic reduction in lumen diameter would be considered part of the microcirculation. Such a definition would include the smallest arteries and arterioles in the microcirculation in addition to capillaries and venules (68).

A primary function of the microcirculation is to optimize the delivery of nutrients and removal of waste products from all cells of the body in response to variations in demand (113). A second important function is to avoid large fluctuations in hydrostatic pressure at the level of the capillaries that otherwise would impair capillary exchange. Finally, it is at the level of the microcirculation that a substantial proportion of the drop in hydrostatic pressure occurs. The microcirculation is, therefore, extremely important in determining the overall peripheral resistance (68).

In normal conditions, systemic, regional, and local metabolic and myogenic autoregulatory mechanisms ensure adequate progress of these microcirculatory functions (60, 113). In pathological conditions (e.g., obesity), however, the loss of such mechanisms results in the development of microvascular dysfunction.

Microvascular Dysfunction in Obesity

Evidence from several studies indicates that obesity impairs microvascular function in several ways. First, impairments of endothelial function of different microvascular structures have been demonstrated in obesity. Obese subjects showed blunted vasodilation in response to classic endothelium-dependent vasodilators in skin and resistance arteries (24, 29, 101). In addition, obese individuals showed diminished vasodilator function of resistance vessels and capillary recruitment to reactive hyperemia (6, 24, 29, 41) and shear stress (6). Of great interest are observations on insulin-mediated control of tissue perfusion. Over a decade ago, Laakso et al. (64) drew attention to the decreased sensitivity of resistance vessels to insulin-induced endothelium-dependent vasodilation in obese individuals. Others have confirmed this

observation in the microcirculation of the skin, using nailfold capillairoscopy (29). In addition to abolished insulin-induced vasodilation in resistance vessels, impaired microvascular recruitment during hyperinsulinemia has also been demonstrated (29). The latter is in good accordance with regard to microvascular recruitment in skeletal muscle. Wallis et al. (117) revealed impaired muscle microvascular action of insulin in obese rats, whereas Clerk et al. (21) were the first to demonstrate this in human obesity. In fact, measures of body fatness are strongly related to skin microvascular function even in lean individuals (27, 94). Second, in addition to these functional changes, structural impairments of the microvasculature have been demonstrated in obesity. The skeletal muscle circulation of obese Zucker rats shows decreased capillary density, so-called rarefaction (40, 42), and structural remodeling (103). Recent studies of obese individuals have also demonstrated this capillary rarefaction in human skeletal muscle (46, 107). There is convincing evidence that this reduction in microvessel density in obesity may be most accurately predicted by the reduced bioavailability of vasodilative agents (i.e., endothelial dysfunction) in obesity. However, the mechanisms through which this endothelial dysfunction-related reduction in skeletal muscle microvessel density evolves have not been fully elucidated (43). Some studies suggest that insulin, acting on the insulin and IGF receptors, in concert with angiotensin II (AngII) stimulates vascular remodeling (see also remodeling in hypertension below) (51).

In accord with a causal role for obesity in the pathogenesis of endothelial dysfunction, weight loss was found to improve endothelial function (131). It can be concluded that a clear association between obesity and microvascular dysfunction, possibly via the endothelium, in different tissues has been established.

Microvascular Dysfunction and Hypertension

In most forms of hypertension, cardiac output is close to normal, and the peripheral vascular resistance is increased in proportion to the increase in blood pressure. Since the major drop in hydrostatic pressure occurs in precapillary vessels ranging from 300 to 10 μm in diameter, i.e., the smallest arteries and arterioles, these vessels represent the principal site of the increased resistance in hypertension (68).

Hypertension is characterized by functional as well as structural changes in this microvasculature (68). First, the mechanisms regulating vasomotor tone may be abnormal, leading to enhanced vasoconstriction or reduced vasodilatation (55). Second, decreases in arteriolar diameters and increases in the wall-to-lumen ratio of small arteries have been demonstrated (55, 68, 104). Third, a reduction in the density (rarefaction) of arterioles, venules, and capillaries can be observed in different vascular beds (55, 56, 92, 104). Since the Hagen-Poiseille's law shows that the resistance of a blood vessel is related to the inverse of the fourth power of vessel diameter, it can be appreciated that small reductions in diameter have significant consequences for vascular resistance (104).

It has been known for many years that increased wall-to-lumen ratio and microvascular rarefaction can be viewed as a result of increased vascular pressure. Among the factors that initiate this remodeling are endothelial dysfunction, changed blood flow, and increased transmural pressure. Since the endothelium serves as a pressure sensor and integrates signals to the underlying vascular smooth muscle cells, it plays an important role in this remodeling process. In addition, an increasing number of studies have shown that AngII is an important factor that stimulates vascular remodeling. Via multiple signalling pathways, AngII induces synthesis of growth factors and pro-inflammatory mediators, which lead to vascular injury and structural remodeling (109).

Besides being the consequence of hypertension, there is also evidence that these microvascular abnormalities may precede the elevation in blood pressure. A smaller retinal arteriolar diameter has been shown to prospectively predict the development of hypertension (57, 122). With regard to rarefaction, Le Noble et al. (67) found a structural rarefaction of capillaries and small arterioles in muscle of spontaneously hypertensive rats even in the absence of a substantial elevation in blood pressure. Human studies have demonstrated that patients with mild borderline primary hypertension showed as much skin capillary rarefaction as those with established hypertension (5). In addition, impaired microvascular vasodilation and capillary rarefaction were associated with a familial predisposition to essential hypertension (75). Furthermore, capillary density has been found to correlate inversely with blood pressure in hypertensive, normotensive lean, and normotensive obese subjects (29, 92, 94).

Thus microvascular abnormalities in obesity may contribute to the development of hypertension. Furthermore, a "vicious cycle" may exist in which the microcirculation maintains or even amplifies increased blood pressure in obesity.

Microvascular Dysfunction and Insulin Resistance

Insulin resistance is typically defined as decreased sensitivity for insulin-mediated glucose disposal. A major action of insulin in muscle and adipose tissue involves translocation of the insulin-responsive glucose transporter (GLUT4) to the cell surface, leading to glucose uptake in peripheral tissues. This requires phosphatidylinositol (PI3)-kinase-dependent signaling pathways (63).

In addition to this metabolic action, insulin has two discrete actions on the arterial vasculature to promote the delivery of insulin and glucose to skeletal muscles. In the 1990s, Baron and colleagues were the first to report insulin's ability to vasodilate resistance vessels and consequently increase total skeletal muscle blood flow (8, 9). It was demonstrated that this increase in bulk blood flow was paralleled by an increase in insulin-mediated glucose uptake (11, 64).

Although several studies have confirmed this vascular action of insulin (15, 25, 105), some studies have failed to observe changes in total flow with insulin (19). Part of this discrepancy can be explained by subject factors as limb muscularity and physiological fitness. However, the duration and dose of the insulin infusion seems also to be important (123). In most studies, insulin-induced increases in total limb blood flow are only observed using supra-physiological doses of insulin or after several hours delay when physiological concentrations are used (128). Moreover, insulin-mediated changes in glucose uptake often precede insulin-mediated changes in leg blood flow, and studies during hyperinsulinemia and manipulation of total limb blood flow with different vasodilators have shown that total limb blood flow can be increased without any changes in insulin-mediated glucose uptake. As a consequence, the physiological importance, in stimulating glucose uptake, of insulin's ability to increase total blood flow is doubtful (128).

Besides these actions on resistance vessels, insulin induces a second vascular action further down the arterial tree, termed functional capillary recruitment. By reducing precapillary arteriolar tone and/or altering arteriolar vasomotion, insulin redirects blood flow within the microvascular bed from non-nutritive to nutritive vessels, with a resultant increase in the overall number of perfused capillaries. Given that the nutritive capillary bed is directly involved in nutrient delivery to muscles, an increase in blood volume of the nutritive capillary bed directly enhances access of glucose and insulin to muscle tissue (19, 63).

Insulin-induced functionally capillary recruitment has been shown to require physiological concentrations of insulin with a time course that approximates the time course for insulin-mediated glucose uptake in skeletal muscle (63, 115, 123). Rattigan et al. (87) were the first to report this insulin-mediated capillary recruitment within the skeletal muscle of a rat's hind limb. In subsequent in vivo rat studies, this insulin-induced effect on capillary perfusion was further established (17, 86, 116, 128). In human muscle, it was shown that insulin increased microvascular blood volume (21, 22, 84). Moreover, hyperinsulinemia was shown to enhance skin post-occlusive capillary recruitment and microvascular vasomotion in human skin and muscle (26, 93).

In support of the physiological importance of insulin-induced capillary recruitment, several studies have demonstrated a strong relationship between capillary recruitment and skeletal muscle glucose uptake (22, 29, 86, 93, 115). In addition, specific inhibition of insulin-mediated microvascular effects causes a concomitant 30–40% reduction in glucose disposal (10, 114, 115). This indicates a functional coupling between insulin-induced effects on muscle microvascular perfusion and glucose uptake. This link is underscored by the fact that the vascular actions of insulin are established through stimulation of PI3-kinase-dependent insulin-signaling pathways that bear striking similarities to the metabolic insulin-signaling pathways (63). Both human and rat studies underline this coupling. Obese Zucker rats are characterized by both impaired insulin-induced glucose uptake and impaired capillary recruitment in the basal state and during hyperinsulinemia (117). In human obesity, similar impairments have recently been demonstrated (21, 28, 29, 64).

These findings suggest the involvement of microvascular dysfunction in the development of obesity-related insulin resistance. In terms of cause and effect, there is support for the suggestion that microvascular dysfunction precedes and even predicts the development of insulin resistance and Type 2 diabetes (71, 72, 122). This idea is also supported by studies showing endothelial dysfunction in mildly overweight, normoglycemic subjects with a strong family history of Type 2 diabetes mellitus (13).

Possible Mechanisms for Obesity-Associated Microvascular Dysfunction

There may be several mechanisms involved in the development of obesity-associated microvascular dysfunction. In the following subsections, we will discuss two main mechanisms.

Intracellular signaling

The metabolic action of insulin to stimulate glucose uptake in skeletal muscle and adipose tissue is mediated through stimulation of PI3-kinase-dependent signaling pathways. These pathways involve the insulin receptor, insulin receptor substrate 1 (IRS-1), PI3-kinase, phosphoinositide-dependent kinase 1 (PDK-1), and protein kinase B (Akt) (63). The vasodilator actions of insulin require highly parallel PI3-kinase-dependent insulin-signaling pathways. Insulin-induced stimulation of Akt directly increases endothelial NO synthase (eNOS) activity, leading to increased NO production (63, 82) (FIGURE 1).

In addition to its vasodilator actions, insulin also has vasoconstrictor effects. These vasoconstrictor effects are mainly mediated by the vasoconstrictor peptide endothelin-1 (ET-1) (63). ET-1 is produced in the vascular endothelium through stimulation of the intracellular MAP-kinase signaling pathway and the extracellular signal-regulated kinase-1/2 (ERK1/2)

(35). The PI3-kinase pathways are not involved (FIGURE 1). Thus insulin has opposing endothelial-derived vasodilating and vasoconstrictor effects, with the net effect being dependent on the balance between these two. Normally, the net result is either neutral or vasodilatory.

Obesity-associated microvascular dysfunction may be caused by cellular defects that influence this balance. First, obesity is associated with an increased production of reactive oxygen species (ROS) (30, 65, 80). ROS limits the bioavailability of NO via reduced NO production and direct inactivation of NO by superoxide (O_2^-) (66). Second, muscle and kidney eNOS expression and activity are diminished in obesity (50, 69, 89, 111, 124), resulting in blunted NO production. Finally, the intracellular insulin signaling transduction pathway is impaired (119). Fatty acid elevation induces phosphorylation of IRS-1 that interferes with insulin-receptor mediated phosphorylation of IRS-1, and in turn results in impaired activation of PI3-kinase (97). As a consequence of these cellular defects, endothelium-derived vasodilation, including insulin-mediated dilation, is blunted in obesity.

In contrast, the signaling pathways for insulin-mediated vasoconstriction seem to be intact or only selectively impaired in obesity. Cardillo et al. (14) demonstrated impaired MAP-kinase pathway activity in obese rats, whereas Jiang et al. (59) showed intact MAP-kinase pathways in the vasculature of obese Zucker rats. However, ERK1/2 activation remains intact in obesity (59). Therefore, insulin-induced vasoconstriction can be demonstrated. In line with this, insulin induced ET-1-dependent vasoconstriction has been shown in skeletal muscle arterioles of obese rats (36).

Thus there is an imbalance between NO and ET-1 production in obesity, wherein the vasoreactivity is shifted from vasodilation toward vasoconstriction. This is further demonstrated in Cardillo's study in which obese, hypertensive individuals showed insulin-induced vasoconstriction and increased ET-1-dependent vasoconstrictor tone as well as decreased NO-dependent vasodilator tone (14, 48). This endothelial dysfunction may contribute importantly to obesity-associated insulin resistance and obesity-associated hypertension.

Endocrine signaling

Adipokines. The fact that measures of adiposity and microvascular function are closely linked is strongly suggestive for signaling pathways between adipose tissue and the microcirculation. Adipose tissue functions not merely as a passive storage depot but as a highly active endocrine organ. Adipose tissue, and in particular visceral adipocytes, secrete a variety of bioactive substances called adipokines. In the case of obesity, there is an enhanced production of free fatty acids (FFA) (81), angiotensinogen, leptin, resistin, and several inflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin-6 (IL-6) (52, 99, 121, 127), whereas the production of adiponectin, an anti-inflammatory adipokine, is reduced (7).

FFA and TNF-α elevation impair insulin sensitivity and increase blood pressure through mechanisms that are not completely understood but do involve microvascular function (20, 28, 125). In lean rats, acute FFA elevation impairs insulin-mediated capillary recruitment and muscle glucose uptake (20). In addition, human studies also demonstrate endothelial dysfunction in response to FFA exposure. Steinberg et al. (102) and Watanabe et al. (120) demonstrated a reduction in endothelium-dependent vasodilation with intralipid infusion in resistance vessels. In another study, elevation of FFA levels in lean subjects resulted in impaired basal and insulin-induced skin capillary recruitment and endothelium-dependent vasodilation, which was associated with reduced glucose uptake. Conversely, obese women showed improved basal and insulin-mediated skin capillary recruitment and glucose uptake in response to lowering FFA levels (28). In this study, approximately 29% of the effects of FFA elevation or lowering on insulin-induced glucose uptake could be explained by changes in microvascular function, which is consistent with a role for FFA-induced microvascular dysfunction in the development of obesity-associated disorders (28).

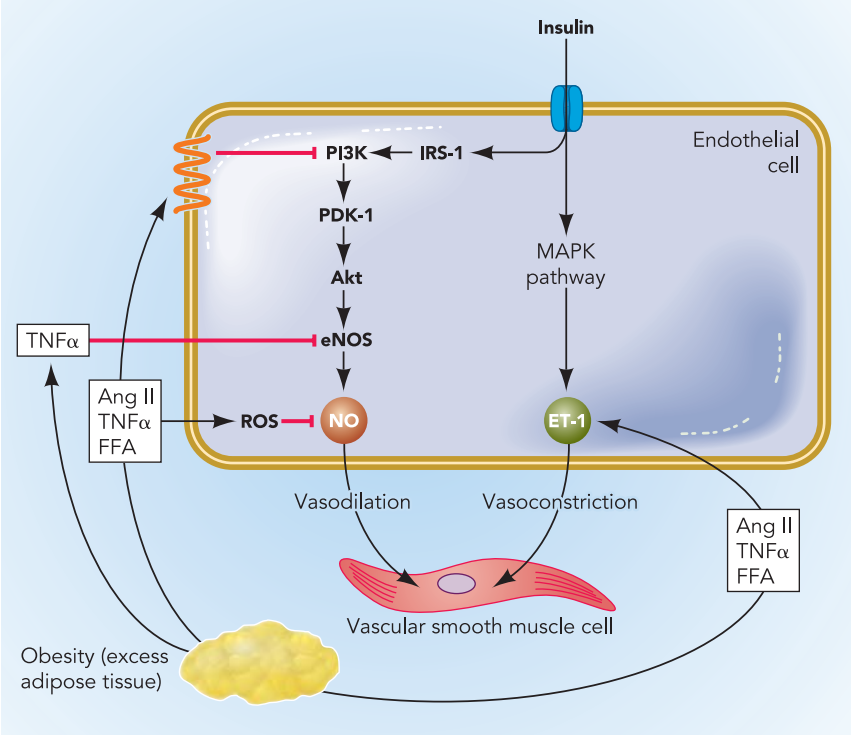

FIGURE 1. **Mechanisms of insulin-mediated nitric oxide and endothelin 1 production**
Mechanisms of insulin-mediated nitric oxide (NO) and endothelin 1 (ET-1) production leading to vasodilation and vasoconstriction, respectively. Angiotensin II (AngII), tumor necrosis factor α (TNF-α), and free fatty acids (FFA) inhibit the PI3-kinase (PI3K) pathway and stimulate the MAPK pathway. IRS-1, insulin receptor substrate 1; PDK-1, phosphoinositide-dependent kinase 1; Akt, protein kinase B; eNOS, endothelial nitric oxide synthase.

The mechanisms by which circulating FFAs impair basal and insulin-mediated effects on microvascular function are not completely understood. First, elevation of FFA blunts insulin-induced PI3-kinase activation in human muscle (31, 97, 119) and in cultured cells (62, 118) (FIGURE 1). Second, FFA elevation induces an increase in ROS production (70). Third, FFA elevation may cause vascular endothelial dysfunction indirectly via increased release of the vasoconstrictor substance ET-1 (81).

Increased production of the proinflammatory cytokine TNF-α is associated with obesity-related insulin resistance and hypertension (54, 79, 108). It has been suggested that the vasculature is an important target of TNF-α (125, 129). Indeed, in a rat in vivo clamp study, acute administration of TNF-α has been shown to inhibit insulin-mediated increases in femoral blood flow and muscle capillary recruitment, leading to a marked decrease in insulin sensitivity. The inhibitory effect of TNF-α appeared to be wholly hemodynamic in that insulin-mediated increases in femoral blood flow and capillary recruitment were totally blocked (125). Furthermore, in a human study, weight loss resulted in significant amelioration of endothelial function that closely correlated with a reduction in circulating TNF-α (131).

Circulating TNF-α may impair insulin-mediated effects on microvascular function by impairing the balance between endothelial-derived vasodilator and vasoconstrictor substances. TNF-α downregulates the expression of eNOS (85, 124) and upregulates ET-1 expression in human endothelial cells (73). Furthermore, it may directly activate NAD(P)H oxidase and increase ROS production in the endothelial and vascular smooth muscle cells (30, 58). More importantly, adipose tissue-derived TNF-α may suppress insulin-mediated hemodynamic and metabolic effects through inhibition of IRS-1 phosphorylation (53, 121). In addition to these direct effects of TNF-α, TNF-α may also induce microvascular dysfunction indirectly through stimulation of lipolysis, thereby leading to an increased release of FFAs (FIGURE 1).

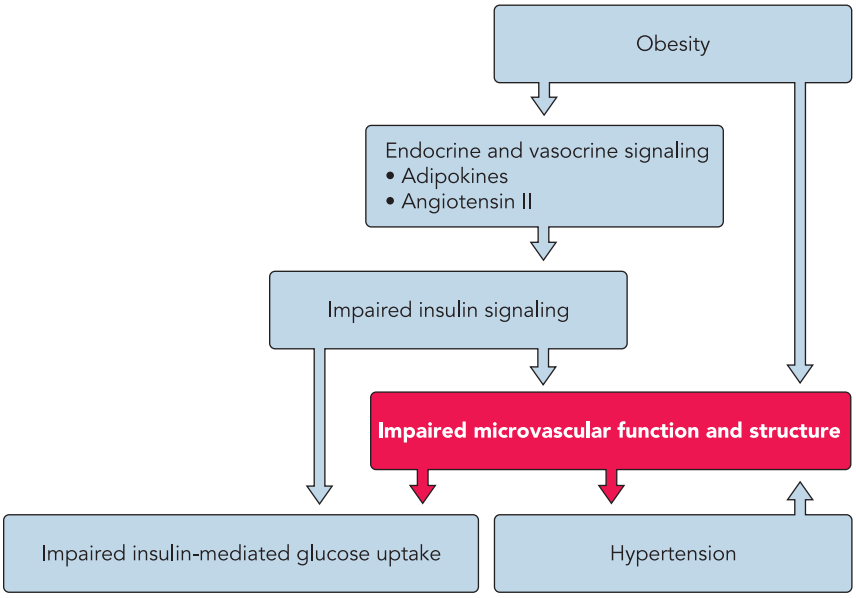

FIGURE 2. **The hypothesised relationships between obesity, microvascular function, hypertension, and impaired insulin-mediated glucose uptake**
Impaired microvascular function may play a central role in the development of obesity-related disorders.

Leptin is another adipocyte-derived hormone that rises with increasing percentage of body fat (99, 121), which is likely to be the result of resistance to its appetite-suppressing effects in obesity. Leptin plays an important role in vascular physiology, as leptin signaling in skeletal muscle activates various kinases including PI3-kinase (32). Therefore, decreased leptin signaling leads to impaired insulin-induced microvascular function and, as a consequence, decreased insulin-mediated glucose uptake. Furthermore, increased levels of leptin have been shown to increase ROS production in endothelial cells (99).

Adiponectin is unique amongst the adipokines in that increasing fatness is associated with a lower concentration (7). Adiponectin affects glucose uptake and vascular endothelium via increased phosphorylation of IRS-1 and other molecules in the insulin-signaling cascade (16).

In conclusion, several adipose tissue-derived factors, in particular FFA and TNF-α, influence insulin signaling and, thereby, insulin-mediated vasodilation. These endocrine factors therefore provide a potential link between obesity-associated microcirculatory dysfunction and obesity-related hypertension and insulin resistance.

Besides these endocrine factors linking obesity to impaired insulin-induced vasodilation, recently a vasoregulatory role for local deposits of fat has been postulated (126). Obese Zucker rats are characterized by a well circumscribed depot of fat cells around the origin of the nutritive arteriole supplying the cremaster muscle, whereas lean rats are not. Adipokines released by these fat cells may inhibit directly vasodilatory pathways distal in the arteriole and thereby cause loss of blood flow in the nutritive capillary network supplied by this arteriole. In this hypothesis, adipokines released from fat depots have local rather than a systemic vasoregulatory effect, a mechanism that is termed "vasocrine" signaling.

The renin-angiotensin system. Recent evidence suggests that the renin-angiotensin system (RAS) is another important system involved in microvascular functioning and, consequently, the development of insulin resistance. All the components of the RAS necessary to generate the vasoconstrictor AngII are expressed in human adipose tissue (61, 91). Increased activity of the RAS has been demonstrated in obesity, both systemically and within adipose tissue, and this may relate directly to the mass of adipose tissue (12, 83). Furthermore, a reduction in body weight leads to a reduced RAS activity in plasma and adipose tissue

that parallels a fall in blood pressure (33, 110). Given that weight loss reduces systemic RAS activity, adipose tissue RAS components may have paracrine and endocrine functions. This is further supported by the fact that adipose-tissue derived AngII not only binds to receptors on adipocyte plasma membranes but also to presynaptic nerve endings and blood vessels (34).

In healthy subjects, infusion of the vasoconstrictor AngII causes a redirection of blood flow between different vascular beds and within the skeletal muscle vascular bed. This redistribution leads to an increase in total muscle blood flow and capillary recruitment, which as a result increases insulin-induced glucose uptake (18, 38). In contrast, in obesity, the RAS seems to have a detrimental effect on insulin-induced glucose uptake, and activation of the RAS contributes to obesity-associated hypertension (98, 110). Studies have shown increased pressor responses to AngII in rat and men with (visceral) obesity (4, 76, 95). In addition, a rat study demonstrated that AngII-induced hypertension is associated with endothelial dysfunction (45). In addition, chronic AngII administration in rats caused insulin resistance in muscle and adipose tissue (44, 76), whereas blocking the RAS improved insulin sensitivity in muscle of diabetic mice (96). Moreover, several large-scale clinical trials have demonstrated that AngII subtype 1 (AT1) receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEi) decreased the risk for new-onset diabetes mellitus in hypertensive patients by about 25% (2). Whether these protective effects of RAS blockade are attributable to improvements in microvascular function requires further study. Both ACEis and ARBs have been shown to enhance blood flow in peripheral tissues such as skeletal muscle (74, 77). A study in humans showed that a FFA-induced impairment in the endothelial function was completely prevented by a single dose of either an ARB or an ACEi, which suggests that an elevation of FFAs induces endothelial dysfunction through activation of the RAS (120).

Several studies have been conducted to elucidate the mechanisms by which RAS activation impairs endothelial function. First, AngII stimulates phosphorylation of IRS-1 (39, 112), a process that interferes with insulin-dependent activation of PI3-kinase, resulting in inhibited glucose uptake and NO synthase (100). Second, AngII is a well known stimulant of ROS production causing an increased degradation of NO (44, 45, 76, 130). Indeed, recent studies indicated a reduced production of ROS in humans and rats using the ARB valsartan (23, 96). Third, AngII stimulates the production of ET-1 in the endothelium (78, 106) (FIGURE 1). Fourth, AngII is known to have a number of proinflammatory effects, such as the release of inflammatory cytokines (51). For example, incubation of muscle with AngII increased TNF-α secretion (108), whereas an ARB or ACE-I decreased skeletal muscle TNF-α (96). Finally, it has been proposed that AngII exhibits anti-adipogenic actions, thereby inhibiting adipocyte differentiation and elevating FFA levels. Indeed, blocking the AT1 receptor stimulates adiopogenesis (90).

To summarize, these data suggest an important role for AngII in compromising microvascular function and thus provide another potential link between obesity and insulin resistance and hypertension (FIGURE 2).

"These endocrine factors therefore provide a potential link between obesity-associated microcirculatory dysfunction and obesity-related hypertension and insulin resistance."

Conclusion

Obesity is an important risk factor for insulin resistance and hypertension and plays a central role in the metabolic syndrome. A better understanding of the pathophysiology of the syndrome may lead to new therapeutic approaches. It is therefore of great importance to unravel the underlying mechanisms. This paper has reviewed the evidence for an important role for the microcirculation as a possible link between obesity, insulin resistance, and hypertension.

Obesity is associated with several impairments in the microcirculation, including rarefaction and impaired endothelial function. It has been demonstrated that these microvascular dysfunctions not only increase peripheral vascular resistance and blood pressure but also decrease insulin-mediated glucose uptake, and therefore provide a link between obesity and obesity-related disorders. This microvascular dysfunction may be the result of alterations in intracellular and endocrine signaling, in which the RAS may play a prominent role. The detrimental effects of RAS activation on microvascular function in obesity may provide an explanation for the protective effect of RAS blockade for the development of Type 2 diabetes mellitus. ■

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