Cross Talk Between Adipose Tissue Cells: Impact on Pathophysiology

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The metabolic functionality of adipose tissue is intimately dependent on local communication between various cell types. It influences not only the equilibrium between lipogenesis and lipolysis but also between hypertrophic and hyperplastic growth, thereby determining the role adipose tissue plays in the insulin resistance syndrome.

White adipose tissue developed during our evolution to enable us to operate independently of continuous food intake. It therefore constitutes an essential part of the body by meeting its metabolic needs. If present in excessive quantities, however, it may also be at least partly responsible for diseases clustered in the insulin resistance syndrome. This review will discuss as yet neglected details of white adipose tissue homeostasis and speculate about their impact on physiology and pathology.

Although endocrine hormones and nervous stimulation rapidly regulate white adipose tissue metabolism according to the current needs of the body, paracrine and autocrine factors determine the cellularity and metabolic responsiveness of the tissue. Both tissue cellularity and metabolic responsiveness are intimately dependent on the cross talk between the cells making up white adipose tissue, i.e., preadipocytes, adipocytes, vascular endothelial cells, and vascular smooth muscle cells.

Physiology of white adipose tissue cells

Metabolically active white adipose tissue is characterized by small but numerous adipocytes connected to an extensive capillary network (5). Compared with other tissues of the body, white adipose tissue can change very drastically in cellular composition and size throughout life, depending on the subject’s energy state. When individuals ingest more energy than they use up, white adipose tissue grows by recruiting new adipocytes from the adipose precursor cell pool (hyperplasia) and by enlarging existing adipocytes through deposition of more intracellular lipid (hypertrophy). Recruitment of new adipocytes is always accompanied by a close spatial and temporal development of blood vessels, whereas hypertrophy of fat cells evokes no changes in the vasculature (5). During shortage of nourishment, adipocytes release their triacylglycerols in the form of free fatty acids and glycerol. Under extreme fasting conditions, they give up all stored lipid and are no longer visually distinguishable from preadipocytes. Just as with hypertrophy, the number of blood vessels is unchanged during hypotrophy (Fig. 1).

Substrate supply to and from the adipocyte must necessarily be transported via the systemic vasculature. Therefore, white adipose tissue microvasculature is well developed: fat cells are always associated with blood vessels, and the degree of white adipose tissue vascularity and vascular wall permeability is greater than that of skeletal muscle (5). Average blood flow to white adipose tissue can vary from 3 to 30 ml-min⁻¹·100 g tissue⁻¹. This wide range is the consequence of a relatively constant basal perfusion per adipocyte (20–30 pl/min) and the great differences in cell number per unit weight (5). Both lipid deposition and lipolysis are closely controlled by the adipocyte’s blood supply. Lipoprotein lipase, for example, is synthesized within the adipocyte and then secreted to its active site on the capillary endothelium. It controls the supply of fatty acids derived from circulating triacylglycerols to the fat cell. The capillary endothelial surface can thus become limiting for hypertrophy of the cell. Free fatty acid mobilization from the adipocyte is equally dependent on its blood supply: increased blood flow serves to transport serum albumin to the tissue in sufficient quantity to allow for increased removal of free fatty acids. On the other hand, a high ratio of free fatty acids to serum albumin leads to vasoconstriction and subsequent reesterification of free fatty acids to triacylglycerols (5).

Preadipocyte proliferation, adipose conversion, and the regulation of adipocyte size are under autocrine, paracrine, and endocrine control. Many of the factors secreted by cells in white adipose tissue not only act locally to influence proliferation, growth, and metabolism but also contribute to whole body homeostasis in an endocrine fashion. A good example for this is leptin, a proteohormone expressed and secreted by adipocytes, which exerts autocrine/paracrine actions on adipocytes (reduction in lipid synthesis) as well as endocrine actions on the central nervous system (most notably reduction in appetite), the pancreatic islets (depletion of the tissue’s lipids and therefore inhibition of the insulin production in β-cells), and other organ systems (18).

Numerous recent reviews focus on white adipose tissue as an endocrine gland and the endocrine regulation of the tissue’s functions (see Ref. 18 for an example). Here we want to put emphasis on the autocrine/paracrine interplay of local factors within the adipose organ. One should always keep in mind, however, that all internal cross talk between adipose tissue cells is influenced by and itself influences other tissues on the endocrine level.
Local communication in adipose tissue

Cell-cell communication can take place through direct contact, surface molecules, the extracellular matrix, and soluble molecules. During white adipose tissue development, preadipocytes and vascular endothelial cells are believed to be in very close contact, maybe even sharing continuous plasma membrane leaflets (5). During the development from preadipocytes to adipocytes, however, the individual cells develop an envelope of extracellular matrix similar to a basement membrane, so direct cell-cell contact becomes impossible. Communication now has to depend on soluble molecules and matrix interactions. Table 1 shows most of the secreted, soluble effectors with mainly autocrine/paracrine functions in white adipose tissue that are known today. Factors with mainly endocrine actions (like leptin, estrogen, and plasminogen activator inhibitor-1) as well as those that belong more or less directly to metabolism (like lipoprotein lipase, cholesteryl-ester transfer protein, retinol binding protein, and free fatty acids) have been omitted. For a more detailed discussion in the text, an exemplary fraction of these tissue hormones has been chosen. Obviously, these represent only the tip of an iceberg that will undoubtedly be looked at more comprehensively in the future.

Individual factors looked at separately. Angiotensin (ANG) peptides are cleaved from circulating or locally produced angiotensinogen. The first peptide to emerge is ANG I, which is devoid of biological activity. It can be cleaved to ANG II by angiotensin-converting enzyme, which is present on preadipocytes, adipocytes, vascular endothelial cells, and vascular smooth muscle cells, or to ANG 1–7 by neutral endopeptidase, which is expressed on vascular endothelial cells (7). ANG II is a potent vasoconstrictor through direct actions on vascular smooth muscle cells and inhibits adipose conversion of preadipocytes (16). ANG 1–7 stimulates vascular endothelial cells to secrete nitric oxide (NO) and prostacyclin, leading to vasodilatation, possibly by potentiating the action of kinins (14).

Kinins are derived from kininogen by the action of kallikrein. It is still unresolved whether kininogen and kallikrein are acquired from the circulation or if they are locally produced. The circulating kallikrein kinin system can be activated on vascular endothelial cells, but studies with rat adipocytes also indicate a local production. Kinins elicit NO and prostacyclin secretion from vascular endothelial cells and are therefore potent vasodilators (14). They also increase the permeability of the endothelium and lead to marked enhancement of the insulin sensitivity of adipocytes (4).

Endothelin is produced in vascular endothelial cells through cleavage of proendothelin to big endothelin and subsequent conversion to endothelin by endothelin-converting enzyme (13). Endothelin is secreted mainly abuminally and acts in a paracrine and autocrine fashion on cells in its immediate vicinity (13): vascular smooth muscle cells respond with long-lasting constriction, whereas vascular endothelial cells react with short-term release of NO and prostacyclin, although vasodilatation predominates in adipose tissue vasculature. Endothelin is a strong inhibitor of preadipocyte differentiation (10) and induces insulin resistance in adipocytes (17).

NO is liberated in white adipose tissue by preadipocytes, adipocytes, vascular endothelial cells, and vascular smooth muscle cells (8, 14). The enzymes responsible are endothelial NO synthase (eNOS) in vascular endothelial cells and adipocytes and the inducible NO synthase (iNOS) in all cell types when appropriately stimulated. Constitutive expression of iNOS, albeit at low levels, in white adipose tissue can be put down to the fact that tumor necrosis factor (TNF)-α is expressed and secreted by adipose cells. NO can activate soluble guanylate cyclase and interacts, depending on the redox species, with redox metal-containing proteins and/or with thiol groups of proteins (8). High concentrations of NO inhibit lipolysis stimulated by different pathways, depending on the NO species (NO+, NO , NO 1–7). NO+ increases basal lipolysis, whereas NO* and NO show no effect on basal lipolysis. Low levels of intracellular NO, on the other hand, are necessary for both basal and stimulated lipolysis, because they keep protein kinase A in an active state due to NO’s antioxidant-related properties (8). NO is also responsible for blunting the TNF-α-stimulated lipoprotein lipase-activity and uncoupling protein-

FIGURE 1. Changes in white adipose tissue mass and cellularity. VSMC, vascular smooth muscle cells; VEC, vascular endothelial cells.
Thus NO appears to function to keep adipocytes in their present status, inhibiting lipolysis and energy dissipation as well as lipogenesis. In addition to its effects on adipocytes, NO is a strong vasodilator in vascular smooth muscle cells (14) and takes part in signaling processes leading to angiogenesis in vascular endothelial cells (15).

Looking at each factor individually does not give a true picture of their physiological significance. The following part of this review will therefore deal with how these local effectors interact on multiple levels to mediate white adipose tissue homeostasis.

**Tissue factor interplay to keep adipose tissue cellularity unchanged.** When energy intake equals energy expenditure, white adipose tissue should neither shrink nor grow. This adipose tissue homeostasis is dependent on a balance between locally generated growth stimulators and growth inhibitors whose biological properties neutralize one another to maintain a zero-sum balance on tissue turnover. In contrast to other tissues, in which cell proliferation is the only possible mode of tissue enlargement, local effectors have to be further separated into hyperplastic growth stimulators/inhibitors and hypertrophic growth stimulators/inhibitors.

In principle, three major regulatory mechanisms operate in white adipose tissue: opposing effects are elicited by one and the same factor, simultaneously present inhibitors and stimulators antagonize each others' actions, and amplifying cycles lead to a coordinated rise in factors with similar actions. The following examples illustrate the complexity that governs tissue homeostasis, without any claim to be exhaustive.

If opposing effects are elicited by the same factor, the resulting net effect is determined by the potency of stimulation, time, and the context of other factors present. ANG II, for example, whose biological properties neutralize one another to maintain a zero-sum balance on tissue turnover. In contrast to other tissues, in which cell proliferation is the only possible mode of tissue enlargement, local effectors have to be further separated into hyperplastic growth stimulators/inhibitors and hypertrophic growth stimulators/inhibitors.

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### TABLE 1. Local effectors in white adipose tissue

<table>
<thead>
<tr>
<th>Produced by</th>
<th>Effects on Preadipocytes</th>
<th>Effects on Adipocytes</th>
<th>Effects on VEC</th>
<th>Effects on VSMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine</td>
<td>Differentiation</td>
<td>Antilipolysis, insulin sensitivity</td>
<td>Angiogenesis, apoptosis, reduced permeability</td>
<td>Vasodilatation</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Adipocytes</td>
<td>Lipogenesis</td>
<td>No proliferation</td>
<td></td>
</tr>
<tr>
<td>ANG II</td>
<td>Preadipocytes, adipocytes, VEC, VSMC</td>
<td>Lipogenesis in 3T3-L1 cells</td>
<td>Apoptosis</td>
<td>Proliferation, vasoconstriction</td>
</tr>
<tr>
<td>ANG 1–7</td>
<td>VEC</td>
<td>No proliferation</td>
<td>No proliferation, endothelium-dependent vasodilatation</td>
<td></td>
</tr>
<tr>
<td>ASP</td>
<td>Adipocytes</td>
<td>Lipogenesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bFGF</td>
<td>Preadipocytes, adipocytes, VEC, VSMC</td>
<td>Proliferation</td>
<td>Angiogenesis</td>
<td>Antiapoptotic/proliferation, migration</td>
</tr>
<tr>
<td>CNP</td>
<td>VEC</td>
<td>Lipolysis</td>
<td>Less proliferation</td>
<td>Vasodilatation, no proliferation</td>
</tr>
<tr>
<td>Endothelin</td>
<td>VEC</td>
<td>No differentiation</td>
<td>Insulin resistance, no lipogenesis*</td>
<td>Vasoconstriction, proliferation</td>
</tr>
<tr>
<td>IGF</td>
<td>Preadipocytes, adipocytes, VEC, VSMC</td>
<td>Proliferation, differentiation</td>
<td>Lipogenesis</td>
<td>Vasodilatation, proliferation</td>
</tr>
<tr>
<td>Interleukin-6</td>
<td>Adipocytes, VEC</td>
<td>Lipolysis, less lipogenesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kinins</td>
<td>Adipocytes, VEC</td>
<td>Insulin sensitivity</td>
<td>Permeability</td>
<td>Endothelium-dependent vasodilatation</td>
</tr>
<tr>
<td>Monobutyrin</td>
<td>Adipocytes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitric oxide</td>
<td>Adipocytes, VEC, VSMC</td>
<td>Differentiation</td>
<td>Antilipolysis</td>
<td>Angiogenesis</td>
</tr>
<tr>
<td>PDGF</td>
<td>VEC</td>
<td>Proliferation,* no differentiation</td>
<td>Angiogenesis</td>
<td>Proliferation</td>
</tr>
<tr>
<td>PGI2</td>
<td>Preadipocytes, Adipocytes, VEC, VSMC</td>
<td>Differentiation*</td>
<td>Antilipolysis</td>
<td>Vasodilatation</td>
</tr>
<tr>
<td>PGE2</td>
<td>Adipocytes</td>
<td></td>
<td></td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Preadipocytes, Adipocytes, VEC, VSMC</td>
<td>Proliferation, no differentiation</td>
<td>Lipolysis</td>
<td>Angiogenesis</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Adipocytes</td>
<td>Proliferation, no differentiation</td>
<td>Lipolysis, insulin resistance</td>
<td>Permeability</td>
</tr>
</tbody>
</table>

VEC, vascular endothelial cells; VSMC, vascular smooth muscle cells; ANG, angiotensin; ASP, acylation-stimulating protein; bFGF, basic fibroblast growth factor; CNP, C-type natriuretic peptide; IGF, insulin-like growth factor; PDGF, platelet-derived growth factor; PGI2, prostacyclin; PGE2, prostaglandin E2; TGF, transforming growth factor; TNF, tumor necrosis factor. The exact concentration of most of these factors in white adipose tissue remain elusive due to technical problems. *Contrary effects have been observed in the murine 3T3-L1 cell line.
being a potent inhibitor of preadipocyte differentiation and thus hyperplastic growth (16), can provoke adipose conversion indirectly through stimulation of prostacyclin secretion from adipocytes and vascular smooth muscle cells. The same is true for ANG II-elicted vasoconstriction, which increases the reesterification of previously liberated free fatty acids, an effect that is counterbalanced by a secondary rise in prostaglandins and NO from adipocytes, vascular endothelial cells, and vascular smooth muscle cells (14). If prostaglandin production is downregulated, for instance by elevated circulating insulin levels, the antiadipogenic and constrictive actions of ANG II are bound to be stronger. As a second example, prostaglandins show strong antilipolytic effects whenever the Gi pool of the adipocyte is fully available. Shortage of Gi, which could be caused by elevated adenosine levels and a great number of activated adenosine receptors, might lead to Gi coupling of prostaglandin receptors and subsequent enhancement of lipolysis (9). The vasodilator C-type natriuretic peptide, on the other hand, upregulates endothelin receptors in vascular smooth muscle cells, potentiating its vasoconstrictor effect on these cells.

Endothelin and bradykinin are a representative pair of antagonistic factors. Endothelin, commonly recognized as a powerful vasoconstrictor, can only exhibit this effect if kinin levels are not elevated; and although bradykinin acts as a potent insulin sensitizer for adipocytes (4), endothelin causes insulin resistance in the same cells (17).

ANG II and endothelin amplify each other’s production and effects. Endothelin stimulates angiotensin-converting enzyme activity, thus leading to a rise in tissue ANG II concentration. ANG II, on the other hand, stimulates endothelin expression, consequently elevating endothelin levels (2).

Enzyme activities that determine the local tissue factor balance. The tissue level of the individual factors is determined by their rate of production and degradation. Both production and degradation are catalyzed mainly by three proteolytic enzymes, namely angiotensin-converting enzyme, endothelin-converting enzyme, and neutral endopeptidase (Fig. 2). Angiotensin-converting enzyme cleaves ANG I to produce active ANG II, converts ANG 1–7 to ANG 1–5, and cleaves active bradykinin 1–9, rendering inactive bradykinin 1–7. Endothelin-converting enzyme mainly activates big endothelin to endothelin but can also inactivate bradykinin. Neutral endopeptidase is involved in the metabolism of many peptides: ANG I is cleaved to active ANG 1–7, and bradykinin, ANG II, C-type natriuretic peptide, and endothelin are inactivated (13). Both ANG II and endothelin are potent inhibitors of adipose conversion and thus of hyperplastic growth (10, 16). They also lead to vasoconstriction, counteracting net lipolysis, because liberated free fatty acids cannot be transported to other tissues and are consequently reesterified. Angiotensin-converting enzyme and endothelin-converting enzyme activities can hence be expected to steer adipose tissue in the direction of hypertrophy, accompanied by elevated basal lipolysis, insulin resistance, and elevated vascular resistance. Inhibition of angiotensin-converting enzyme and/or endothelin-converting enzyme activity should therefore lead to smaller fat cells in white adipose tissue with lower basal lipolysis, a greater insulin suppression of lipolysis, and lower peripheral resistance. Figure 3 shows a schematic representation of these adjustments taking place in white adipose tissue during angiotensin-converting enzyme inhibition.

Experimental support comes from studies in rats and humans. In the rat, a higher angiotensin-converting enzyme activity was found in the epididymal than the perirenal adipose tissue depot, probably causing the differences in growth pattern between the two depots: epididymal white adipose tissue is characterized by an early plateau in the recruitment of new adipocytes, whereas perirenal white adipose tissue can accumulate new fat cells throughout the life span of the rat (6). Angiotensin-converting enzyme inhibition during the development of young rats leads to reduced growth of white adipose tissue mass with lower fat cell volume but equal or even increased fat cell numbers (6). Some other studies did not find the reduction in white adipose tissue mass, but they did not look at fat cell volumes. It can be assumed that in these animals increased hyperplastic adipose tissue growth compensated for a decreased triacylglycerol accumulation per cell.

In humans, angiotensin-converting enzyme inhibition is accompanied by a marked enhancement of insulin suppres-
sion of lipolysis (3). Angiotensin-converting enzyme inhibition results in elevated bradykinin levels and lower endothelin concentrations, which shifts the ratio of the insulin sensitizer bradykinin to insulin desensitizer endothelin toward more bradykinin and less endothelin. Basal free fatty acid levels are not directly affected by a change in the ratio of bradykinin to endothelin. A change in adipose tissue cellularity from large to small fat cells is necessary to lower basal lipolysis. During several clinical studies, basal plasma free fatty acids were unchanged or suppressed by angiotensin-converting enzyme inhibition, depending on the time scale of the experiment. No effects were observed during acute angiotensin-converting enzyme inhibitor administration, whereas treatment over a period of several months led to suppression of plasma free fatty acids (3). This argues for the above-mentioned change in adipose tissue cellularity, because basal lipolysis is enhanced in hypertrophic adipocytes and development of a greater number of small adipocytes is associated with lowered plasma free fatty acid concentrations through an enhanced uptake into these cells. Changes in angiotensin-converting enzyme activity are not associated with changes in body composition in humans (3), indicating that the increased hyperplastic adipose tissue growth may have compensated for the decrease in fat cell hypertrophy in humans as in rats. Combined endothelin-converting enzyme and angiotensin-converting enzyme inhibition would be expected to intensify these changes (13).

The effect of changes in neutral endopeptidase activity cannot be as easily predicted, because both hypertrophic and hyperplastic factors are degraded (13). Although neutral endopeptidase inactivates the vasoconstrictors ANG II and endothelin, it also inactivates the vasodilators ANG 1–7 and bradykinin. On the adipocyte level, neutral endopeptidase could be expected to lead to a diminished prostacyclin production, because both inductors ANG II and bradykinin are degraded. The production of ANG 1–7 depends not only on neutral endopeptidase activity but also on angiotensin-converting enzyme, because a high rate of ANG II production depletes the ANG I pool available for conversion to ANG 1–7 (14). Neutral endopeptidase inhibitors have not yet been tested with respect to their effects on adipose tissue, and prediction of the outcome is difficult.

White adipose tissue homeostasis can only be achieved during times of steady-state energy flux. Modern civilizations, however, favor a net energy balance that is positive, which leads to overall growth in fat stores. Although a great number of clinical trials have shown the association of obesity with metabolic and hemodynamic alterations. This is indeed true, as seen in persons treated with thiazolidinediones. These insulin-sensitizing drugs lead to enhanced overall adipose tissue growth but convert hypertrophic to hyperplastic subcutaneous adipose tissue with a greatly enhanced number of small adipocytes and a significant decrease in large fat cells. Although adipose tissue mass is markedly elevated in thiazolidinedione-treated patients, insulin resistance as well as the accompanying dyslipidemia are significantly ameliorated (1). Whereas thiazolidinediones are artificial substances, factors occurring naturally in the body are also able to alter the way of adipose tissue growth, as seen above. Understanding the interplay of local effectors that determine the size and number of adipocytes in a given fat depot can thus lead to a more profound understanding of adipose tissue’s role in the insulin resistance syndrome. Individuals with a high ratio of the hypertrophic factors ANG II and endothelin to the hyperplastic factors kinins, prostaglandins, NO, and ANG 1–7 can be expected to exhibit a greater ratio of hypertrophic to hyperplastic adipose tissue growth during positive energy balance and therefore to be at a greater risk of metabolic and hemody-

**When adipose tissue growth becomes a problem**

From the physiological/pathological point of view, adipose tissue growth per se is not harmful to whole body homeostasis. Efficient storage of triacylglycerols in times of nutritional surplus has been selected for in evolution and is still an advantage for physically active individuals. Grossly elevated fat stores of the hypertrophic type have, however, been associated with the development of dyslipidemia, insulin resistance, and hypertension (12). Although the causal relationship has not been satisfactorily elucidated and is probably highly complex, hypertrophic adipose tissue is always associated with far worse metabolic and hemodynamic consequences than hyperplastic adipose tissue (12). Consequently, a change from hypertrophic to hyperplastic white adipose tissue should ameliorate these metabolic and hemodynamic alterations. This is indeed true, as seen in persons treated with thiazolidinediones. These insulin-sensitizing drugs lead to enhanced overall adipose tissue growth but convert hypertrophic to hyperplastic subcutaneous adipose tissue with a greatly enhanced number of small adipocytes and a significant decrease in large fat cells.
namic disorders. Next we discuss this issue in greater detail with respect to each individual disorder.

**Dyslipidemia.** Imbeault et al. (12) showed that subcutaneous abdominal fat cell weight was the best independent variable predicting plasma triacylglycerols and low-density lipoprotein-apolipoprotein B levels in humans. They concluded that, for a given visceral white adipose tissue deposition, the presence of hypertrophic subcutaneous abdominal adipocytes appears to be associated with further deterioration of the metabolic risk profile.

**Insulin resistance.** Hennes et al. (11) discovered that resistance to the antilipolytic actions of insulin, a characteristic of hypertrophic adipocytes, distinguishes abdominally obese hypertensives from normotensive obese and normal weight subjects, a relationship that is independent of visceral adipose tissue mass. They attribute the insulin resistance to a more active angiotensin-converting enzyme because angiotensin-converting enzyme inhibition not only lowered blood pressure but also significantly improved insulin-resistant lipolysis.

**Hypertension.** The relationship between adipose tissue expansion and blood pressure is most complex. Weight gain per se always leads to increased cardiac output and blood volume. This increase is compensated for by a reduction in peripheral resistance through neovascularization of the new tissue mass. Thus weight gain only leads to a rise in blood pressure if the simultaneous increase in cardiac output is not fully compensated for. Adipose tissue is generally a low-resistance tissue compared with resting muscle. If weight gain were achieved by hyperplastic white adipose tissue growth, then the concomitant development of blood vessels would result in an expanded vascular tree capable of dispersing the elevated blood volume. If, however, adipose tissue mass were elevated mainly through increased adipocyte cell size, new vessels would not form and the resulting obesity hypertension would be characterized by elevated cardiac output and inappropriately normal peripheral resistance. This is indeed the distinguishing feature of obesity-induced hypertension compared with hypertension in a lean person. Insulin-resistant lipolysis in white adipose tissue might therefore be circumstantial evidence for hypertrophic adipose tissue growth in those obese individuals that have developed hypertension due to the inability to lower peripheral resistance in the face of weight gain-induced elevated cardiac output.

**Conclusions**

Adipose tissue is no exception in that its growth and cellular composition is tightly regulated by a large selection of local effectors. The exact level at which these factors reach a balance might differ among individuals, with potentially far-reaching consequences: during positive energy balance, easily achieved in today’s civilizations, persons with a more hypertrophic type of adipose tissue expansion will experience a greater risk of metabolic and cardiovascular complications than those individuals with a more hyperplastic tissue growth. It has already been stressed by many investigators that successful therapeutic intervention in obesity or any of the associated diseases has to be selected with its potential influence on adipose tissue in mind. If adipose tissue mass cannot be kept within reasonable limits, a change in itscellularity might be equally beneficial. Detailed studies concerning this issue are clearly needed.

We apologize to many investigators whose work we were unable to cite because of space limitations.

**References**


