and after more than 6 months of NCPAP treatment. Long-term NCPAP treatment had a significant effect on the abdominal fat deposits.

Thus, OSAS has significant effects on the blood coagulation system, cardiac sympathetic nerve function, the levels of heat shock protein 72 expression, and lipid metabolism, which could in turn have a significant correlation with the morbidity of several diseases. Therefore, when obesity-linked disorders are investigated, it is important to consider the existence of OSAS in these obese patients because the prevalence of OSAS is so high (1, 2).


References


3. Role of Adipocytokines on the Pathogenesis of Atherosclerosis in Visceral Obesity

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Abstract

Obesity which is defined as accumulation of excess body fat, is a major cause of atherosclerotic vascular disease in industrial countries. Recent advances in the biology of adipose tissue have revealed that adipose tissue is not simply an energy storage organ but it also secretes a variety of molecules which

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Adipocytokines and Visceral Obesity

Visceral fat syndrome as a multiple risk factor clustering syndrome

Obesity, the accumulation of excess body fat, is a major risk factor for diabetes mellitus, hyperlipidemia, hypertension and atherosclerotic diseases in industrialized countries. Recent advances in obesity research have revealed that body fat distribution rather than the total amount of fat is related to obesity-linked disorders. Kisselah et al (1) reported upper body obesity, accumulation of fat in the abdominal portion had higher plasma triglyceride and glucose levels than lower-body obesity accumulation of fat in the hip and lower extremities. Larson et al (2) reported in a prospective study, that the waist to hip ratio is an independent risk factor for coronary artery disease (CAD). We developed a method to evaluate body fat distribution using computed tomography. This method enabled us to estimate the amount of intra-abdominal visceral fat located in the mesenterium and omentum. The ratio of visceral fat area to subcutaneous fat area (V/S) was closely correlated with plasma triglyceride, cholesterol and glucose levels in obese subjects (3). Moreover, V/S was significantly correlated with systolic or diastolic blood pressure in premenopausal obese women. Thus, visceral obesity is frequently accompanied by obesity-linked disorders.

Visceral fat accumulation is seen even in people whose body mass index is within the normal limit. Approximately 40% of the patients with CAD showed accumulation of visceral fat greater than 100 cm². These individuals possessed multiple coronary risk factors such as hypertension, glucose intolerance and dyslipoprotein-emia (4). Thus, visceral fat accumulation is the feasible condition of CAD through the development of multiple risk factors. We proposed the concept of "visceral fat syndrome" as a multiple risk factor clustering syndrome. Visceral fat syndrome is a condition compatible with other insulin resistance syndromes such as "syndrome X" proposed by Reaven (5) or "deadly quartet" syndrome proposed by Kaplan (6). However, the molecular mechanism related to why visceral fat accumulation causes multiple disorders listed in these syndromes has not been elucidated.

Portal adipose tissue and hyperlipoproteinemia

One of the characteristics of visceral fat is that this fat tissue is located upstream of the liver via the portal vein. Since the visceral fat has high lipogenic and lipolytic activity, a large amount of free fatty acids (FFAs) released from visceral fat is drained into the liver. FFAs may influence the gene expression of the proteins on lipoprotein synthesis in the liver. We investigated mRNA levels of acyl CoA synthetase (ACS) and microsomal triglyceride transfer protein (MTP) in Otsuka Long Evans Tokushima Fatty (OLETF) rats, an animal model of visceral fat syndrome. ACS activates free fatty acids to acyl CoA and acyl-CoAs are used for triglyceride synthesis. MTP mediates the assembly of triglyceride and apolipoprotein B (apo B) and facilitates secretion of very low density lipoprotein (VLDL) particles.

OLETF rats had a larger quantity of visceral fat, higher levels of portal FFAs and higher levels of plasma triglyceride compared to their lean littermates. Hepatic ACS activity, ACS mRNA levels, and MTP mRNA levels in OLETF rats were higher than their lean littermates. Thus, in the condition of visceral fat accumulation, VLDL secretion is enhanced not only by the increase of triglyceride substrates but also by induction of ACS and MTP genes (Fig. 1) (7). Recently, FFAs have been shown to act like a hormone through the action of the nuclear receptor, peroxisome proliferator activated receptors (PPARs). In the case of ACS gene, FFAs enhance the transcriptional level by the binding of PPARα to its promoter. Administration of oleic acid to cultured Hep G2 cells increased MTP mRNA levels. Thus, a mechanism similar to that of ACS gene may operate in MTP gene.

Expressed genes in adipose tissue

To elucidate further characteristics of visceral fat, we analyzed the gene expression profile in visceral and subcutaneous fat by collaboration with Dr. Okubo and Dr. Matsubara of Osaka University. Figure 2 shows the prevalence list of known genes classified by their functions. Unexpectedly, adipocyte tissues, especially visceral fat expressed a lot of genes for secretory proteins (8). In recent years, adipocyte has been shown to secrete various biologically active molecules. Adipsin is a Factor D, a member of the complement system. Spiegelman’s group has shown that TNFα is related to insulin resistance in obesity (9). Friedman’s group cloned leptin gene, whose product participates in the regulation of body weight (10). These molecules acting on the homeostasis of whole body can be summarized as "adipocytokines". We found plasminogen activator inhibitor type 1 (PAI-1) gene in the visceral fat cDNA library.

The fibrinolytic system is regulated by multiple factors. PAI-1 inhibits the action of the plasminogen activator, and thus inhibits the formation of plasmin. An elevated level of plasma PAI-1 represents a condition for thrombotic tendency. Adipose tissue contains various types of cells including endothelial cells, which are known to express PAI-1 gene. To elucidate whether the adipocyte itself expresses PAI-1 gene or not, we investigated PAI-1 gene expression in 3T3 L1 adipocytes by Northern blot analysis (11). PAI-1 mRNA was detected in 3T3 L1
Figure 1. Possible mechanism of hyperlipidemia in visceral fat syndrome.

Figure 2. Prevalence of expressed genes in subcutaneous and visceral fat tissues.
preadipocytes and was upregulated after differentiation into adipocytes. Changes in the PAI-1 mRNA levels in adipose tissue during the development of obesity were investigated in ventromedial hypothalamus (VMH)-lesioned rats. PAI-1 mRNA levels increased up to 10-fold in the visceral fat but remained unchanged in the subcutaneous fat. The relation between the plasma PAI-1 level and the amount of abdominal fat was investigated in human subjects. Plasma PAI-1 level was not significantly correlated with subcutaneous fat area. In contrast, the plasma PAI-1 level was positively correlated with visceral fat area. These data suggested that the secreted PAI-1 from accumulated visceral fat may contribute to the determination of plasma PAI-1 levels and thus, may have an important role in the development of thrombotic disorders frequently found in visceral obesity and syndrome X.

**Location-specific control of the genes in adipose tissues**

Next, we investigated the durational changes of the leptin mRNA levels; this is another cytokine secreted from adipose tissue in VMH rats (12). Leptin mRNA abundance increased very rapidly in the visceral fat and reached a steady state level. In contrast leptin mRNA increased at later stage in the subcu-

![Graph showing relation between fat cell size and mRNA levels of PAI-1 and leptin](image)

**Figure 3. Relation between fat cell size and mRNA levels of PAI-1 and leptin.** ○: leptin, ●: PAI-1.

![Diagram showing pathogenetic mechanism of visceral fat syndrome](image)

**Figure 4. Schematic outline of pathogenetic mechanism of visceral fat syndrome.**
taneous fat and a 10-fold increase was observed at 15 days after VMH destruction. The plasma level of leptin was well correlated with subcutaneous fat area in humans. However, no significant increase was found in non-obese men with various amounts of visceral fat (13). Thus, the amount of subcutaneous fat contributes to the determination of the plasma leptin level more profoundly than visceral fat. Figure 3 shows the relation between fat cell size and the abundance of PAI-1 and leptin mRNA in adipose tissues of VMH rats. In visceral fat, leptin mRNA abundance increased very rapidly and reached the steady state level very quickly. PAI-1 mRNA levels were elevated with the increase of cell size. In subcutaneous fat, leptin mRNA increased dramatically with cell size but PAI-1 mRNA remained unchanged. Thus, these two genes in each adipose tissue are regulated in a different manner.

Adiponectin, a novel adipose-specific seretory protein

To discover a novel adipocytokine, we isolated a full length cDNA for the gene most abundantly expressed in adipose tissue (14). The adipose most abundant gene transcript-1 (apM1) cDNA encoded 244-amino-acids open reading frame and long 3'-untranslated region. Amino terminus of the predicted protein contained putative signal sequence motif followed by a short stretch of collagen-like domain appearing glycine residue every 3 amino acids. The carboxy terminus after the collagen-like domain possessed significant homology with collagen X, VIII and complement factor C1q. The expression of apM1 mRNA was restricted to white adipose tissue. Therefore, the apM1 gene product is the third adipose-specific secretory protein; together with adipsin and leptin. We termed this matrix-like protein exclusively produced by adipose tissue as “adiponectin”. The physiological function of adiponectin has not been elucidated.

We demonstrated that visceral fat accumulation is a feasible condition for the development of various human diseases. Visceral fat tissue produces and secretes various biologically active molecules (Fig. 4). FFAs secreted from visceral fat up-regulates hepatic genes for lipoprotein synthesis and are possibly related to hyperlipidemia. PAI-1 is related to thrombotic disorders commonly found in visceral fat obesity. A new adipose-specific protein, adiponectin, having a collagen-like motif may be related to human disorders. Adipocytokines produced by the accumulated in visceral fat may be a causative factor in the development of various features in visceral fat syndrome.

References