Perivascular adipose tissue AT is a critical regulator of vascular function, which until recently has been greatly overlooked. Virtually all arteries are surrounded by a significant amount of perivascular adipose tissue, which has long been considered to serve primarily a supportive, mechanical purpose. Recent studies show that both visceral and perivascular fat is a very active endocrine and paracrine source of inflammatory cytokines and adipokines. The latter include beneficial adipocytokines such as adiponectin or so far unidentified adipocyte derived relaxing factor (ADRF) as the presence of perivascular AT may decrease contractile responses to vasoconstrictive agents. However, in pathological states such as obesity, hypertension, diabetes metabolic syndrome and other cardiovascular disorders perivascular tissue becomes dysfunctional and production of protective factors diminishes while detrimental adipocytokines such as leptin, resistin, IL-6, TNF-alpha or IL-17 increases. Moreover the dysfunction of perivascular fat can lead to imbalance between vascular nitric oxide (NO) and superoxide production. Adipokines also regulate immune system as chemokines (such as MIP-1 or RANTES) and induce inflammation with infiltration of T cells and macrophages to the vessel wall. Interestingly central nervous system can affect vascular function through mediation of perivascular adipose tissue dysfunction. In particular sympathetic nervous system endings are present in both visceral and perivascular AT. This powerful relationship between the brain and the vessel can be termed "brain-vessel axis" in which - we propose in the Review - perivascular adipose tissue may take center stage. The role of perivascular fat in the regulation of blood vessels depends on metabolic state, inflammation and clinical risk factors. In health protective and vasorelaxant properties of perivascular AT dominate while in pathology pathogenetic influences including neural stimulation of sympathetic nerve endings or humoral effects of certain hormones and adipocytokines dominates. We propose to term this state "perivascular adipose tissue dysfunction" in similarity to endothelial dysfunction.

Key words: perivascular adipose tissue, inflammation, immune regulation, superoxide, nitric oxide, central nervous system, cytokines
INTRODUCTION

Virtually all arteries are surrounded by a significant amount of perivascular adipose tissue, which has long been considered to serve primarily a supportive, mechanical purpose. Recent studies however clearly show that adipose tissue is a very active endocrine and paracrine organ. While the majority of studies relate to typical visceral adipose tissue (VAT) the peri-vascular adipose tissue (VascAT) is also an important source of adipocytokines as well as typical inflammatory cytokines (1, 2, 3). The role of perivascular adipose tissue in the regulation of vascular function and thus in cardiovascular disease is being currently unraveled. Moreover it appears that perivascular fat differs substantially from typical visceral AT both in the states of health and disease. This difference results not only from its direct location next to vascular wall but also from most likely a differential release of adipocytokines and cytokines. The latter however has not yet been fully addressed and defined.

Important studies indicate that VascAT may play a dual role which has been addressed recently in an excellent review by Y. Gao (2). Some of the paracrine factors released from VascAT such as adiponectin have been identified as novel vascular relaxing factors derived from the adipose tissue, which could thus act protectively against hypertension and other vascular related disorders. The exact mechanisms of vasorelaxant actions of adiponectin are incompletely understood. Studies leading to the discovery of this novel vasorelaxant molecule have been initiated by a finding of Soltis and Cassis that the presence of perivascular AT may decrease contractile responses to vasoconstrictive agents such as phenylephrin and norepinephrin (4). At that time however nitric oxide and its role in the regulation of vascular function was at the central stage of vascular biology, thus this report was not fully appreciated until the release of vascular relaxing factor was reported to be produced by VascAT (5). These studies were further advanced by several interesting investigations such as those of Gollasch (1, 3, 5, 6) and Gao (2, 7, 8).

The identity of this substance remains undefined, in spite of numerous suggestions that share similar properties with leptin or adiponectin. These findings however are difficult to understand from the point of view of vascular pathology, and particularly pathology of obesity. Is it possible that adipose tissue, including VascAT, which increases in obesity, could play a protective, anti-hypertensive or anti-atherosclerotic role? Alternatively can we talk about the dysfunction of VascAT in the states of vascular pathologies, similar to endothelial dysfunction in a way that dysfunctional tissue will produce different products, negatively affecting vascular tension and function. These mechanisms however remain to be identified.

The role of VascAT in the regulation of vascular function may finally be also related to the fact that adipose tissue metabolism and release of adipocytokines may be regulated by the central nervous system (CNS). In particular sympathetic nervous system endings are present in VAT but even more abundantly in VascAT.
At the same time it is known that central nervous system can regulate vascular function by release of neuromediators, in peri-vascular tissues including the adventitia and perivascular fat. The role of CNS in the latter has been convincingly demonstrated in numerous models of cardiovascular disease, in which disruption of CNS signaling leads to the abrogation of hypertension or atherosclerosis and alleviated vascular and endothelial dysfunction accompanying these states. This powerful relationship between the brain and the vessel can be termed "brain-vessel axis" in parallel to the accepted and well-described relationship between brain and the gut (the "brain-gut axis (11, 12, 13, 14)").

The Janus face of perivascular adipose tissue is emphasized further by the fact that the absence of perivascular fat tissue, which enhances the contractile response of blood vessels to agonists, and an up regulation of vascular Ang II type 1 receptors in A-ZIP/F1 mice (transgenic lipoatrophic), are some of the mechanisms underlying the blood pressure elevation in these lipoatrophic mice (15).

The present Review will focus on the interrelationships between peri-vascular adipose tissue, vascular dysfunction and inflammation as well as the potential role of central nervous system as key components of the "brain-vessel axis".

COMPOSITION OF PERIVASCULAR ADIPOSE TISSUE

Standard histological view of the structure of blood vessel wall comprises of endothelium, media and the adventitia. Majority of systemic blood vessels however, apart from cerebral vasculature, are surrounded by perivascular adipose tissue (Fig. 1). The intimal and medial hypertrophy has been widely described in cardiovascular pathologies and is even clinically used in the assessment of hypertension or diabetic systemic organ damage (in some guidelines almost at the same level as nephropathy or cardiac hypertrophy). The changes of peri-vascular tissues, particularly perivascular fat are very poorly characterized in either hypertension or diabetes. The opposite relationship is better known. For instance obesity, which is associated with excessive perivascular adipose tissue is a known risk factor for cardiovascular disease. The difference in the role of vascular adipose tissue in the regulation of normal vessel homeostasis versus the regulation in pathology remains unclear.

The structure and composition of perivascular adipose tissue differs in different vascular beds. While larger vessels (for instance mouse aorta) seem to be surrounded by both white and brown adipose tissue (Fig. 1), resistance vessels such as mesenteric arteries are buried in the mesenteric visceral white AT (2). These factors and the relationships between the two types of perivascular fat may play important role determining the function of VascAT in vascular homeostasis. White adipose tissue is a typical "storage" AT characterized by lighter color associated with larger fat storage capacity and lower vascularization and metabolic activity (16). In turn the brown AT is metabolically active thermogenerator in
relation to the presence of large numbers of mitochondria, rich in UCP-1, un-
coupling protein 1 (up to 20% of mitochondrial protein) Both types of AT store fat 
although fat vesicles are smaller and multilocular in brown AT, while white 
adipocytes have unilocular nature, of variable size depending on the adiposity.

There are numerous differences between the white and brown adipose tissue 
(16). However it is important to remember that both adipocyte types are an 
important sources of adipocytokines and both are localized in the visceral 
compartment. However an important difference between the two adipose tissue 
types is its innervation (16). Brown AT is particularly densely innervated, 
allowing it to play a potentially important role in the proposed model of "brain-
vessel axis". Indeed brown AT grows when sympathetic nervous system is 
chronically stimulated, in contrast white AT hypertrophies when de-innervated. 
These differences in characteristics and role of white and brown AT may be very 
important in differential role of perivascular fat in the regulation of vascular 
function in health and disease.

PERIVASCULAR FAT - VILLAIN OR PROTECTOR?

The role of perivascular fat in the regulation of vascular function appears to be 
dual. The physiological role of VascAT affecting vascular tone and function has 
been discovered with the observation that when perivascular AT is left on the 
vessel during the ex vivo vascular constriction studies the vasoconstriction of 
aortic rings to norepinephrine is significantly attenuated. However obesity

Fig. 1. Histological cross-
section of mouse aorta 
indicating large amounts of 
peri-vascular adipose tissue. 
E- endothelium/intima; M- 
media; A-adventitia; W-
white adipose tissue; B-
brown adipose tissue.
accompanied by increased perivascular AT is a key pathogenetic factor in vascular disease, indicating that in these conditions the role of perivascular AT may actually promote vascular dysfunction. At the same time as mentioned above lipoatrophic mice, characterized by the loss of perivascular (as well as other compartments) of adipose tissue show spontaneous vascular dysfunction and develop hypertension (15).

Potential protective properties of perivascular adipose tissue?

More recent studies confirmed the inhibitory action of perivascular fat on aortic and mesenteric contractile responses to a variety of vasoconstrictors and the anticontractile effect is directly dependent on the amount of adipose tissue (1, 5). Thus a term adipocyte-derived relaxing factor (ADRF) was created to characterize this interesting substance, as it became apparent that perivascular fat contributes to the maintenance of basal vascular tone (1, 5). ADRF is released in a calcium- and cAMP-dependent manner and its effects are mediated by opening of the ATP-dependent K+ channels (5). In line with these findings, the mesenteric vascular smooth muscle cell (VSMC) resting membrane potential is more hyperpolarized in arterial rings surrounded by fat than in rings without fat. The real biological nature of ADRF remained until recently undefined. Initially it has been thought that leptin, a typical adipocytokine, could be the ADRF as it has been shown in pharmacological ex vivo experiments to directly induce vasodilatation in the aorta and mesenteric arteries in a mechanism of VSMC membrane hyperpolarization, similar to ADRF. Leptin receptors initially described in the hypothalamus (17, 18) and have central effects (19), are indeed present in endothelium and the mechanisms of vasorelaxation are complex comprising both NO-dependent and hyperpolarization dependent pathways (20). In line with these findings in sympathectomized rats, leptin infusion was in fact found to cause hypotension. It is also important to remember that systemic hyperleptinemia via its central effects leads to a decrease in obesity, which through numerous mechanisms could actually improve endothelial function (21). Finally, the varying effects of leptin on nitric oxide and superoxide systems might be related to genetic variability in either leptin receptors or even target molecules which could include eNOS polymorphisms (22, 23), as well as polymorphisms within vascular oxidases (24) or leptin receptors themselves (25). Studies, particularly in animal models, have indicated that acute administration of induced cardiac ischemia in mice subsequently infused with leptin showed reduction in infarct size (26). Leptin deficiency caused left ventricular hypertrophy adjusted for increased BMI in the ob/ob mice studied with restoration of myocyte size and wall thickness with leptin infusion (27), however the effects of changes of body weight and fat content should be remembered in this context and have not been sufficiently taken into account by authors of these studies.
The effects of leptin on endogenous anti-oxidant capacity in human vasculature (28) should also be taken into account although it has not been addressed so far. Thus although some studies could suggest beneficial effects of leptin production in the perivascular adipose tissue, the data are not sufficiently convincing. Moreover it is important to note that significant vaso-relaxant effects of leptin are observed only at very high concentrations, which are not observed in normal physiology or even pathology.

Recently, adiponectin has been identified as an novel vasorelaxing factor, which relaxes mesenteric rings by opening Kv channels. However, adiponectin does not play a role in the paracrine control of vascular tone by perivascular adipose tissue in this vascular bed, as the anti-contractile effects of perivascular fat were similar in mesenteric artery and aortic rings from adiponectin-deficient mice and wild-type mice. Adiponectin knockout mice show increased neo-intimal proliferation in response to vascular injury (29). These data on the potential role of adiponectin in atherosclerosis are further enhanced by findings that adiponectin can prevent atherosclerosis in ApoE knockout mice (30). Similar results were supported in another study which proposed the mechanism of adiponectin-induced vascular protection via EGF and other endothelial growth factors by attenuating endothelial cell proliferation, terming an intriguing concept of the "adipo-vascular axis" (31). Adiponectin decreases human aortic smooth muscle cells growth and migration response to growth factors (31) and decreasing macrophage production of TNF-alpha (32). Clinical studies of cardiovascular disease support these speculations.

A first population-based study looking at the relationship between small-dense LDL particles and adiponectin relationship, found an inverse relationship of low adiponectin levels with smaller LDL densities (33). Another study supported this LDL finding and also found a positive correlation with HDL, independent of age, sex, and BMI (34). Finally certain treatments can affect adiponectin levels thus modifying the role of VascAT in the regulation of vascular function. Oral hypoglycemic agents, particularly pioglitazone, have been studied with an eye to metabolic parameters, including serum adiponectin levels secondary to its known anti-atherogenic effect. Statistically significant increase in adiponectin was detected (35).

Thus release of adiponectin from peri-vascular adipose tissue may be a very important factor in the protective role of this tissue in physiology, irrespectively if it is or is not the ADRF. Beneficial role of adiponectin released from perivascular fat in the regulation of vascular function appears to be much more unequivocal than the studies of leptin discussed above.

In summary, the nature of ADRF, - the paracrine factor responsible for fat dependent diminishing of vasoconstrictions still remains to be defined.

Moreover it has been shown that ADRF similarly to EDRF becomes dysfunctionally regulated in cardiovascular diseases such as hypertension (3). Thus in cardiovascular pathologies the production of these protective adipocytes
derived factors may be reduced. Moreover certain treatments, such as statins may restore these features of perivascular adipose tissue dysfunction.

**POTENTIAL PATHOGENETIC PROPERTIES OF PERIVASCULAR ADIPOSE TISSUE**

While mechanisms described above may be important in maintaining vascular function in physiology, perivascular adipose tissue, as well as adipose tissue in general may cause several pathological changes in the vasculature. These effects are mediated by promoting vasoconstriction, particularly in response to peripheral nerve stimulation.

*Adipocyte derived ROS*

Similarly to adipocytes derived relaxing factors, the identity of the perivascular adipose tissue derived constricting factors are also unknown. One of the possibilities is that superoxide anion abundantly produced by perivascular adipose tissue (Guzik, Harrison; unpublished data) may exert direct vasoconstrictive properties (8). Indeed, adipocytes express several cellular oxidases which makes them an important source of reactive oxygen species (36), which on their own may constrict blood vessels, and at the same time impair the bioavailability of nitric oxide, one of the key regulators of vascular function. Superoxide reacts abruptly with nitric oxide in-activating NO and removing its beneficial, anti-inflammatory and vasorelaxant properties (22, 28, 37, 38, 39, 40, 41, 42, 43). Moreover free radicals may directly modify inflammatory responses and affect macrophage and T cell infiltration. This occurs through MAP kinase and NFkappaB dependent mechanisms (44). Indeed, overexpression of glucose-6-phosphate dehydrogenase (G6PD) in adipocytes stimulates oxidative stress and at the same time regulate inflammatory responses, thus affecting the neighboring macrophages and T cells (45). Adipogenic G6PD overexpression promotes the expression of pro-oxidative enzymes, including inducible nitric oxide synthase and NADPH oxidase, and the activation of nuclear factor-kappaB (NF-kappaB) signaling, which eventually leads to the dysregulation of adipocytokines and inflammatory signals. Furthermore, oxidative stress in adipocytes stimulate macrophages to express more proinflammatory cytokines and to be recruited to the adipocytes; this would cause chronic inflammatory conditions in the adipose tissue of obesity (45). Fat accumulation correlates with systemic oxidative stress in both humans and mice (36). Production of ROS increased selectively in adipose tissue of obese mice, accompanied by augmented expression of NADPH oxidase and decreased expression of antioxidative enzymes. In cultured adipocytes, elevated levels of fatty acids increased oxidative stress via NADPH oxidase activation, and oxidative stress caused dysregulated production of adipocytokines (fat-derived hormones), including adiponectin, plasminogen activator inhibitor-1, IL-6, and monocyte chemotactic protein-1. Finally, in obese
mice, treatment with NADPH oxidase inhibitor reduces ROS production in adipose tissue, attenuated the dysregulation of adipocytokines, and improved diabetes, hyperlipidemia, and hepatic steatosis and potentially vascular dysfunction (36). Thus increased oxidative stress in accumulated fat is an early instigator of metabolic syndrome and that the redox state in adipose tissue is a potentially useful therapeutic target for obesity-associated metabolic syndrome. However differential NADPH oxidase homologues expression and its regulation in obesity and cardiovascular disease in adipose tissue remains to be defined. However these properties of adipose tissue may be regulated also by its metabolic state (46). Potential importance of these enzymes is also related to potential therapeutic use of NADPH oxidase inhibitors and modulators, which were discussed elsewhere (28, 40, 47, 48, 49, 50).

Angiotensin II

Adipocytes express angiotensinogen (52), although the regulation of its expression in cardiovascular pathology remains unknown. cAMP up regulates in vitro angiotensinogen expression and secretion in human adipose tissue and that the induction in angiotensinogen mRNA levels appears to result, at least in part, from positive effects on the DNA binding activity of CRE transcription factors. Further studies are required to determine whether this regulatory pathway is activated in human obesity and to elucidate the importance of adipose angiotensinogen to the elevated blood pressure observed in this pathological state (52). Angiotensin II leads to an increase in superoxide production in vascular cells including vascular smooth muscle cells and endothelial cells. Interestingly Ang II also acts directly back on adipocytes leading to their proliferation and decreased differentiation. Angiotensin II reduced the Adipogenic response of adipocyte progenitor cells, and the extent of the decrease correlated directly with the subjects' BMI (53). The effect of angiotensin II was reversed by type 1 angiotensin receptor antagonist losartan. This response to angiotensin II in omental adipose progenitor cells from obese subjects opens a venue to understand the deregulation of visceral fat tissue cellularity that has been associated with severe functional abnormalities of the obese condition (53). Moreover perivascular adipose tissue has been demonstrated to release substantial amounts of angiotensin II and its metabolites (Ang I, II, III, IV, 1-9, 1-7, 1-5) (54).

Classical adipocytokines

Data currently available do not sufficiently explain whether leptin serves a beneficial or detrimental role in the cardiovascular system in vivo as has been discussed by us previously (55). Pathogenetic role of leptin in the regulation of vascular function in atherosclerosis has been implicated. It has been shown that high fat diet induced neo-intimal proliferation is associated with increased expression of leptin receptor mRNA and protein (56). In contrast to ob/ob leptin
deficient mice fed the same diet that had no vessel involvement despite diabetes, hyperlipidemia, and worsening obesity. Leptin receptor is expressed within atherosclerotic plaques (56) and leptin infusion in the ob/ob mice resulted in luminal stenosis suggesting a direct link between leptin and atherosclerosis (57). This has also been explored in humans, particularly in the WOSCOPS study which prospectively looked at leptin levels before and after a coronary event in Scotland and despite adjustments for age, systolic blood pressure, lipids, BMI, and CRP still retained significance suggesting leptin as an independent risk factor for atherosclerosis (58). There have been several human clinical trials supporting this strong correlation in myocardial infarction (59), coronary artery calcification (60), and stroke (61) suggesting a more definitive relationship between leptin and the development of clinically pertinent coronary lesions.

However, leptin has not been shown to be only an injurious cytokine. Recent studies, particularly in animal models, have indicated that acute administration of induced cardiac ischemia in mice subsequently infused with leptin showed reduction in infarct size (26). Leptin deficiency caused left ventricular hypertrophy adjusted for increased BMI in the ob/ob mice studied with restoration of myocyte size and wall thickness with leptin infusion (27), however the effects of changes of body weight and fat content should be remembered in this context and have not been sufficiently taken into account by authors of that nice study. Other studies have found contradictory results to previously described leptin-induced myocyte dysfunction and in fact found impairment in cardiomyocyte systolic and diastolic function in leptin-deficient ob/ob mice (62).

The effects of leptin on endogenous anti-oxidant capacity in human vasculature (28) should also be taken into account although has not been addressed so far. Moreover leptin levels and expression may be regulated by numerous factors and clinical conditions (63, 64, 65) and also in relation to some bio-physical factors (66).

Studies of chronic infusion of leptin, at levels comparable to obesity, show a dose-dependent increase in arterial blood pressure in rats (67). Similarly, chronic hyperleptinemia causes endothelial dysfunction (68), defined as loss of nitric oxide bioavailability and production by endothelium. In hypertension and in pre-eclampsia (69). Some actions of leptin can be explained by activation of NADPH oxidase system in the vascular wall in a fashion similar to angiotensin II (70). NADPH oxidases have been shown to be critical in the regulation of oxidative stress in human vasculature in different models (50, 71, 72) particularly in relation to risk factors of atherosclerosis, and their activity is directly involved in the pathogenesis of endothelial dysfunction in various cardiovascular disease states (39, 51, 73).

The effects of leptin in the modulation of brain-vessel axis are emphasized by the fact, that it causes a dose-dependent increase in sympathetic nerve activity. This increase has not been sufficient however, to affect blood pressure or heart rate responses (74). It is therefore possible that leptin could simultaneously...
provide a counteracting effect to actually lower or equilibrate blood pressure by simultaneous actions on vascular tissues, brain and immune system. Although it has to be remembered that as discussed above, in sympathectomized rats, leptin infusion was in fact found to cause hypotension. Further studies are still needed to clarify the contributions to vascular phenomenon such as blood pressure regulation, local, and systemic vasodilatatory effects of leptin.

In summary Leptin has proven to be a multi-faceted cytokine, particularly in the cardiovascular system. However, there is much conflicting research in regards to detrimental or positive effects of leptin. There is also a time element that plays a role in leptin's actions - perhaps differences in acute administration (e.g. in reperfusion) versus chronic elevation of leptin levels as seen in obesity, may play a vital role in leptin's intensity of action. Also, concentrations of leptin to determine effects may also factor in these discrepancies, lower dosages versus supra-physiologic levels each contributing in varying degrees.

Resistin is another typical adipocytokine, which has been implicated in cardiovascular pathology.

Resistin role in endothelial function regulation has been relatively poorly defined so far. In an attempt to better clarify resistin's vascular mechanism in coronary vessels, isolated coronary rings and anesthetized dogs were found to have weakened endothelium dependent vasodilatation with bradykinin, indicating some effects on endothelial function (75). However no effects were observed on acetylcholine induced vasodilatation (75). Simultaneously it has been recently reported that resistin can affect the protein expression of several vascular genes via PI3Kp85alpha. It can stimulate the release of PAI-1, vWF, and ET, and down-regulate eNOS. The effect of resistin on PI3K signaling pathway might contribute to the development of endothelial dysfunction (76).

This conflict could indicate that resistin impairs predominantly EDHF - rather than NO- dependent vasorelaxations. No effect was reported on coronary blood flow, arterial pressure, or heart rate (75). Several studies have indicated an angiogenic aspect to resistin in endothelial cells (77), particularly targeting this mechanism to VEGF and MMP upregulation (78).

It is important to point out that resistin effects may be mediated in the vascular tissues by NADPH oxidases in a similar fashion to effects of leptin discussed above (79). However, comparison studies between the mouse and human expression of resistin showed that increased resistin expression occurred with myeloid lines than from adipocytes in a greater extent than in humans (80).

Effects of resistin on cardiovascular biology remain to be fully elucidated in detail yet.

Recent studies suggest that also novel, less typical adipocytokines such as visfatin may regulate vascular function in cardiovascular pathologies. For instance recent clinical study has shown that visfatin levels are significantly associated with endothelial function in patients with type 2 diabetes. Visfatin is negatively associated with vascular endothelial function evaluated by FMD and
creatinine clearance, and positively associated with log urinary albumin excretion (81). Visfatin was also negatively correlated with circulating aldosterone. Pioglitazone therapy for 12 weeks did not affect the plasma visfatin concentration significantly in all diabetic patients, but a significant elevation in visfatin was obtained in women only (81).

INFLAMMATION IN PERIVASCULAR ADIPOSE TISSUE

One of the most prominent observations regarding the role of perivascular adipose tissue in cardiovascular pathologies, are recent observations that in hypertension, as well as in certain models of atherosclerosis, perivascular adipose tissue serves as a harbor for inflammatory cells, particularly T cells, B cells and macrophages. In fact, as we have recently demonstrated in the setting of angiotensin II dependent hypertension T cells infiltrate perivascular fat and adventitia and release cytokine milieu which in turn regulates vascular function and affects blood pressure regulation (82). Interestingly in the setting of certain cardiovascular pathologies adipocytokines are able to chemotactively attract inflammatory cells. Indeed both leptin and resistin have been shown to act chemotactively and perivascular adipose tissue may produce classical chemotactic cytokines as well (83). Moreover both of these adipocytokines may lead to activation of T cells and monocytes, as has been demonstrated both in vitro and in vivo. These aspects of proinflammatory effects of adipocytokines in the setting of vascular disease have been recently reviewed in the Journal (55).

ROLE OF THE CENTRAL NERVOUS SYSTEM IN THE REGULATION OF PERIVASCULAR INFLAMMATION

The central nervous system (CNS) is an organ immunologically distinct, having blood-brain barrier, which protects it from the immunological cells penetration under normal, physiological conditions. Additionally, healthy CNS tissue is devoid of MHC antigens. However, the CNS is important modulator of the immune system function influencing its adaptive response to various stress factors. Lesions of certain areas of the brain, predominantly hypothalamus (HPA) produce either inhibitory or stimulatory effects on the immunological functions. Moreover, the hypophysectomy abolishes this phenomenon (84). Moreover areas of third ventricle, particularly subfornical organ may be important in the regulation of sympathetic activity, which innervates lymph nodes and spleen as well as perivascular adipose tissue.

Lymphocytes and macrophages possess the surface receptors for the numerous neurotransmitters, neuropeptides and neurohormones for example: beta-endorphin, methionone-enkephalin, leucine-enkephalin - opioid family members secreted by neurons (85). Additionally, cytokines produced by the immunological
cells affect HPA function forming the negative feedback-loop. Moreover, the branches of the sympathetic nervous system end in thymus and bone marrow influencing novel immune cell production and they lead the impulses to the secondary lymphoid organs such as spleen, lymph node and Payer’s patches as well as vascular adipose tissue which harbors vascular lymphoid tissue.

The CNS modulates immunological function not only directly but also by controlling the release other substances being known as immunomodulatory such as corticosteroids and catecholamines, which are known as profound immunosuppressants. (Lymphocytes and macrophages have β2-adrenergic receptors on the surface). On the contrary, growth hormone and prolactin are immunoenhancing factors secreted in the pituitary gland. They trigger releasing of IL-1, IL-6 and TNF-alfa from the leukocytes known as acute-phase response agents increasing the inflammation process in the tissue by activation of hepatocytes to synthesize acute phase proteins working as opsonins and by activating bone marrow to produce and release more neutrophils into periphery. All 3 agents are also endogenous pyrogens, raising body temperature by influencing HPA and auxiliary tissues as fat and muscles. TNF-alpha influences also dendritic cell by stimulation their migration to the lymph node and their maturation. Additionally, the CNS increases IL-2, IL-3 and IL-8 production. IL-8 acts mainly as a chemotactic factor recruiting neutrophils, basophiles and T cells to the site of infection. IL-3, being growth factor for progenitor hematopoetic cells, provides production of more leukocytes de novo from bone marrow. Finally, IL-2 is co-stimulatory molecule, which is necessary for T cells efficient proliferation and differentiation.

**BRAIN-ADIPOCYTE AXIS**

The central nervous system (CNS) may not only regulate inflammatory cell activation but also plays a critical role in the regulation of energy homeostasis by closely monitoring food intake, energy expenditure and the status of the body's fat stores (11, 14, 86). The central regulation of food intake is very complex involving multiple neuro-humoral signaling pathways between the brain and the peripheral organs (*i.e.*; stomach, intestine, pancreas, liver). In addition, adipose tissue has emerged over the last decade as an important endocrine organ that plays a key role in the contribution of cardiovascular related diseases. As discussed above, the adipose tissue is capable of synthesizing and secreting several different hormones (adipocytokines), most notably leptin, and it serves as an important metabolic signaling organ that informs the CNS on the nutritional and metabolic status of an individual (86). Obesity is a worldwide epidemic that is partially characterized by the dysregulation of various adipokines. Therefore, the last part of the review will focus on the communication between adipocytes and the brain and how this is altered during obesity and other cardiovascular related diseases.
As a brief overview, the primary component of the CNS responsible for energy homeostasis is the autonomic nervous system (87). This is comprised of two major divisions, the sympathetic and parasympathetic nervous system. The sympathetic nervous system (SNS) exerts its effects either by direct stimulation of sympathetic nerve endings or indirectly via release of catecholamines (epinephrine/norepinephrine) from the adrenal medulla. The SNS is known to have an important role in the regulation of metabolism and the change in its activity has been implicated in the development of obesity and hypertension (10). Studies have shown that obese hypertensive individuals have increased SNS activity (88) and this increased activity may contribute to the increased proliferation of adipocytes as well as secretion of adipokines in hypertensive obese individuals.

The primary regulatory center of the brain responsible for mediating the effects of adipokines and other circulating metabolic hormones is the hypothalamus. Specifically the arcuate nucleus (ARC) is the area within the hypothalamus where various metabolic hormones converge and relay information regarding total energy stores in fat and overall energy availability. The ARC is considered a circumventricular organ which lacks a blood brain barrier thus allowing for the entry of peptides and proteins such as leptin and insulin from the circulation (89). There are two distinct neuronal populations in the ARC that integrate peripheral nutritional and/or feeding signals. One set of neurons located in the ventromedial part of the ARC synthesizes the large precursor protein proopiomelanocortin (POMC) which can be cleaved to melanocyte stimulating hormone (α-MSH), a strong satiety signaling protein that is stimulated by increased circulating levels of leptin and insulin (90, 91). The other important neurons in the ARC are those that synthesize both agouti-related protein (AgRP) and neuropeptide Y (NPY). As opposed to POMC, both AgRP and NPY induce weight gain and promote food intake. Consistent with these roles, protein expression of AgRP and NPY has been shown to be increased during fasting and in Leptin-deficient mice. Overall, the neurons in the ARC serve as important effector sites for peripheral signals such as adipokines and together contribute to the regulation of body weight/energy expenditure.

During obesity several authors have shown that adipokine synthesis and secretion is altered thus leading to an imbalance of the proteins that act on the CNS to regulate food intake/energy expenditure (88, 92, 93, 94). Because obesity is often associated with hypertension, the changes in adipokine levels during obesity most likely play a role in this disease. For example, leptin released from adipocytes has been shown to be increased in obesity and often obese individuals are resistant to leptin actions (74, 95). Moreover, several papers have shown that the effects of leptin are mediated through an increase in sympathetic activity (96). Intracerebral injection of leptin increases sympathetic activation that is similar to systemic administration of leptin and that ablation of the ventromedial nucleus of the hypothalamus prevents
sympathetic responses to leptin (97). These data and others demonstrate the sympathoexcitatory effects of leptin and therefore may explain the increased activity of the sympathetic nervous system during obesity-induced hypertension (98, 99).

A number of studies have shown that adipose tissue is directly innervated by the sympathetic nervous system (100) and this autonomic innervation plays an important role in metabolic (i.e.: thermo genesis) and endocrine functions (i.e.: lipolysis). In addition, some have suggested that the differential distribution and accumulation of body fat (visceral vs. subcutaneous) may be regulated by the sympathetic nervous system (101, 102). Differences in sympathetic innervation and activation of white and brown adipose tissue may contribute to the stimulation/proliferation of adipocytes. Clinical studies have long ago demonstrated that the location of fat deposition is strongly associated with ones risk for cardiovascular disease (103). It is widely accepted that individuals with visceral obesity have a higher risk of cardiovascular disease and mortality than lean non-obese individuals. Furthermore, distribution of fat along the vasculature (perivascular) also appears to play an important role in ones risk for developing cardiovascular disease/metabolic syndrome. Similarly stimulation of vagal nerve may differentially affect adipose tissue distribution and proliferation (104).

However the role of the central nervous system in mediating changes in perivascular fat accumulation is relatively unknown. In addition to subcutaneous and visceral adipose tissue it is quite possible that fat deposition along the vasculature may be partly regulated by changes in the sympathetic nervous system that occur during obesity. Ultimately these changes may contribute to the overall dysfunctional regulation and communication between the "brain-adipocyte" axis during obesity.

SUMMARY

In summary, perivascular adipose tissue appears to be a critical regulator of vascular function, which until recently has been greatly overlooked (Fig. 2). Recent findings show that the role of perivascular fat in the regulation of blood vessels depend on numerous factors, including metabolic state, inflammation as well as clinical risk factors for vascular disease. In health protective and vasorelaxant properties of perivascular adipose tissue dominate while in pathology they are overcome by numerous pathogenetic influences including neural stimulation of sympathetic nerve endings or humoral effects of certain hormones and adipocytokines which may lead to proliferation and activation of adipose tissue. In this setting CNS may stimulate inflammation within the perivascular AT which can directly affect cells within the vessel wall such as endothelium or smooth muscle cells.
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