Abdominal Fat and Sympathetic Overactivity

From Calorie Intake to Postmenopausal Hypertension

Heinz Rupp, Bernhard Maisch[1]

Background: Epidemiologic studies have found an association between overweight and increased mortality arising primarily from cardiovascular disorders. A major determinant is a chronically raised sympathetic nervous system activity which can arise from calorie intake-dependent and -independent mechanisms. Calorie-dependent parameters reflecting sympathetic overactivity are an increased body fat mass and body mass index.

Visceral Fat: Although influenced by calorie intake to a certain extent, visceral fat accumulation is a mechanism which is determined also by estrogen deficiency (postmenopausal hypertension) or enhanced corticoid influences. It is hypothesized that excess catecholamines trigger various adverse processes which, if they persist, can lead or aggravate hypertension and insulin resistance. Visceral but not peripheral fat mass was correlated with atherogenic metabolites.

Excess Catecholamine Syndrome: The present focus on visceral fat accumulation strengthens the concept of an "excess catecholamine syndrome" of which the "metabolic syndrome" appears as one consequence. It is proposed to further assess the potential of transthoracic echocardiography as routine imaging method for the prediction of visceral fat accumulation and its adverse health consequences.

Key Words: Hypertension · Sympathoadrenergic stimulation · Central obesity

Abdominales Fett und Sympathikusüberaktivität. Von der Kalorienaufnahme bis zur postmenopausalen Hypertonie

Hintergrund: Epidemiologische Untersuchungen geben Hinweise auf einen Zusammenhang zwischen Übergewicht und gesteigerter kardiovaskulärer Mortalität. Eine wesentliche Ursache ist eine Steigerung der Aktivität des sympathischen Nervensystems, die nicht nur eine Folge einer erhöhten Kalorienaufnahme sein muss.

Viszerales Fett: Die Folgen einer, bezogen auf die körperliche Aktivität, zu hohen Kalorienaufnahme sind ein gesteigertes Körpergewicht und ein gesteigerter Bodymass-Index, während eine abdominale viszerale Fettansammlung auch auf einem Östrogenmangel bei postmenopausalen Frauen und einem gesteigertem Cortisoleinfluss beruhen kann. Eine chronisch erhöhte Katecholaminfreisetzung führt zu Hypertonie und Insulinresistenz. Im Gegensatz zu peripherem Fett korrelierte eine viszerale Fettansammlung auch mit mehreren atherogenen Parametern.

Exzess-Katecholamin-Syndrom: Die Auswirkungen einer viszeralen Fettansammlung untermauern das Konzept eines „Exzess-Katecholamin-Syndroms", das zu Hypertonie, Insulinresistenz und anderen metabolischen Veränderungen führt, die häufig unter dem Begriff „metabolisches Syndrom" zusammengefasst werden. Vor allem echokardiographische Bestimmungen von epikardialem Fett sollten dazu beitragen, die Zusammenhänge zwischen viszeralem Fett und kardiovaskulären Risiken weiter aufzuklären.

Schlüsselwörter: Sympathisches Nervensystem · Übergewicht · Adipositas · Viszerales Fett · Hypertonie · Insulinresistenz · Katecholamine

[1]Molecular Cardiology Laboratory, Department of Internal Medicine and Cardiology, Philipps University Marburg, Germany.

Introduction

Epidemiologic studies have found an association between overweight and increased mortality arising primarily from cardiovascular disorders. Since the proportion of overweight persons appears to increase steadily in societies with a sedentary lifestyle, therapy of overweight-linked diseases has become a major challenge. Until recently, anthropometric parameters with a prognostic value for cardiovascular morbidity and mortality remained ill-defined. A major progress in identifying overweight-associated cardiovascular disorders came from the determination of localized fat tissues with dual-energy X-ray absorptiometry, magnetic resonance imaging (MRI) and computed tomography (CT) [22]. Among the recent unexpected findings was the observation that pericardial fat accumulation was a stronger coronary risk factor than the other body fat distributions in nonobese men [40]. Moreover, epicardial fat was the strongest independent variable for the severity of coronary artery disease as determined by coronary angiography [14]. Persons with predominant visceral fat accumulation showed also higher epicardial adipose tissue thickness than subjects with predominant peripheral fat distribution [14]. A linear regression analysis showed a good correlation between epicardial adipose tissue and waist circumference and MRI abdominal visceral adipose tissue. Thus, transthoracic echocardiography could be an easy and reliable imaging method for visceral adipose tissue prediction [14].

The need arises, therefore, to better understand pathophysiologic mechanisms associated with the accumulation of different fat tissues. In the present review, evidence is summarized favoring a crucial link between visceral fat accumulation and sympathetic overactivity. Of particular interest, in this respect, is the postmenopausal status which is associated with central fat distribution. Mechanisms will be delineated which link visceral fat accumulation with the progression of hypertension and metabolic disorders. Evidence will be provided which strengthens the concept of the "excess catecholamine syndrome" [28, 29], which represents an early marker of adverse processes underlying the "metabolic syndrome" [27].

Calorie Intake and Sympathetic Overactivity

The sympathetic nervous system activity is modulated by various environmental factors arising from high food abundance and stress [8]. Of crucial importance appears to be calorie intake. Since basal metabolism is determined by sympathetic activity, a close link between calorie intake and energy expenditure is essential. In times of food shortage, the body responds with a reduction in sympathetic activity, heart rate and metabolism which ensures a prolonged survival. Candidates involved in the signaling are insulin and leptin [6, 9]. In rats with chronically implanted pressure transducers, heart rate was linearly correlated with an altered body weight arising from a restricted calorie intake or overfeeding (Rupp, unpublished). It can thus be concluded that a raised heart rate associated with an increased calorie intake represents the consequence of an important principle of energy conservation. Under conditions of a chronically enhanced calorie intake, sympathetic overactivity has, however, adverse effects.

In a number of studies, an increased body mass index (BMI) was associated with a raised sympathetic activity of skeletal muscle [33] and an impairment of reflex sympathetic restraint [11, 12]. Furthermore, kidney norepinephrine spillover was found increased in overweight persons [43]. Of importance is the finding that sympathetic activation occurs already at BMI values < 30 [33]. The view that a raised body weight per se is a crucial determinant of sympathetic overactivity is also supported by experimental data. In animal experiments, an increased calorie intake was associated with a parallel rise in heart rate and blood pressure [31]. The type of diet which raised the calorie intake was identified as a mixture of saturated fat and sucrose. Normotensive rats with implanted radiotelemetry pressure transducers were fed increasing amounts of coconut fat (8%, 16%, and 24%) corresponding to 20–47% of total calories from fat. Thereafter, increasing amounts of sucrose (16%, 32%, and 50%) and fructose (50%) were added to the 24% fat diet corresponding to 13–40% of total calories from sugar. In contrast to the fat diets, the 32% and 50% sucrose diets as well as the 50% fructose diets increased blood pressure and heart rate irrespective of the day-night cycle and the unaltered locomotor activity. Body weight was increased during the 32% and 50% sucrose feedings. The rise in heart rate and blood pressure occurred independently of day-night cycle (Figure 1). Thus, the dip during sleep which is required for maintaining normal vascular structure was prevented by overfeeding the rats. This "hyperkinetic hypertension" associated with body weight gain is a hallmark of a raised sympathetic nervous system activity.

A relationship between body weight increase and rise in sympathetic activity can be inferred also from the finding that younger hypertensive persons exhibit an in-
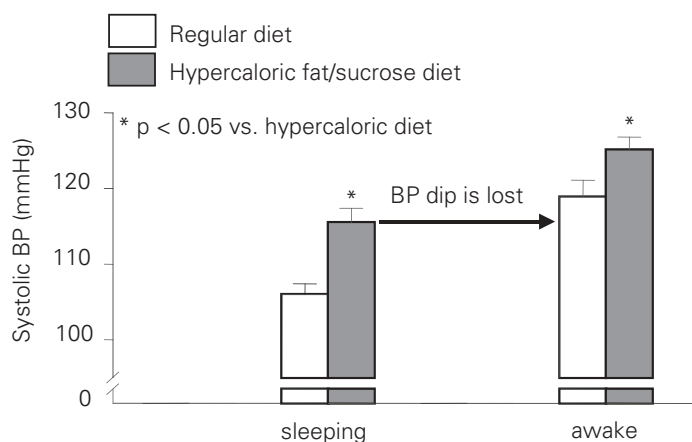
Figure 1. Systolic blood pressure (BP) of normotensive rats fed a hypercaloric diet containing 47% fat and 26% sucrose (% of total calories consumed). Control rats received a 20% fat diet. Blood pressure was recorded by radiotelemetry in conscious rats with chronically implanted pressure transducers. Data are adapted from Rupp & Maisch [31].

Abbildung 1. Systolischer Blutdruck (BP) normotensiver Ratten, die eine hyperkalorische Diät (auf Kalorien bezogen 47% Fett und 26% Saccharose) erhielten. Kontrollratten erhielten eine 20%ige Fettdiät. Der Blutdruck wurde mit Hilfe der Radiotelemetrie und chronisch implantierter Druckaufnehmer gemessen. Die Daten wurden aus Rupp & Maisch [31] übernommen.

creased cardiac output, while the peripheral resistance is, to a great extent, still normal [18]. With increasing age, manifestation of high blood pressure occurs that is based on a progressive increase in peripheral resistance and a gradual normalization of cardiac output [18]. Calorie intake can, however, not easily identify persons who are expected to exhibit sympathetic overactivity.

Visceral Obesity and Sympathetic Overactivity

There is increasing evidence that overweight and particularly obesity should not solely be classified according to the BMI but that the actual distribution of fat involving deep abdominal fat, i.e., visceral fat and subcutaneous abdominal fat, should be taken into account. It has been shown by Alvarez et al. [1] that visceral obesity is associated with a 55% increase in basal muscle sympathetic nerve activity (MSNA) compared with controls matched for total fat mass and abdominal subcutaneous fat. MSNA was more closely associated with abdominal visceral fat than with total fat mass or abdominal subcutaneous fat. It was thus concluded that abdominal fat is an important adipose tissue depot which links obesity with sympathetic neural activation [1]. Among the adiposity indexes, the visceral fat appears thus to provide the best indicator of sympathetic overactivity. General adiposity parameters such as BMI are affected to a greater extent by confounding

influences and are more subject to interindividual variations. It was concluded that the assessment of abdominal fat better identifies the individual at risk of sympathetic overactivity [1].

Central fat mass exhibited a positive and peripheral fat mass a negative correlation with atherogenic and glucose metabolites [35]. It was thus also suggested that a narrow waist and large hips may both protect against cardiovascular disease. Accordingly, a large hip circumference was a strong predictor of health and longevity in women [21]. Large hip and thigh circumferences were also associated with a lower risk of type 2 diabetes that occurred independently of BMI, age and waist circumference. A larger waist circumference was, however, associated with a higher risk [37].

Postmenopausal Transition and Increase in Abdominal Fat

Percent of body fat was related to MSNA in females and males whereby females exhibited a lower level of MSNA at a given body fat [17]. In favor of a crucial role of abdominal visceral fat was the observation that only the waist-to-thigh ratio was an independent predictor of MSNA both in males and females [17].

Of interest, in this respect, is the finding that the postmenopausal status is associated with a preferential increase in intraabdominal fat which is independent of age and total body fat mass [42]. In a prospective study extending over 6 years it was found that women who experienced menopause lost more fat-free mass than women who remained premenopausal [25]. They also exhibited a reduced energy expenditure, an increased waist-to-hip ratio reflecting an increased adiposity. Fasting insulin levels were also increased. A recent cross-sectional study showed that compared with premenopausal women, postmenopausal women had a 49% greater intraabdominal fat which was independent of age and total body fat mass [42] which is also in accordance with previous studies [19, 23].

Hormone replacement therapy had a preventive action on this central fat distribution [39]. In view of the amplifying effect of abdominal fat on sympathetic nervous system activity, it can be deduced that prevention of the postmenopausal fat redistribution blunts the rise in sympathetic activity. Accordingly, elevation of low postmenopausal estrogen levels to physiologic premenopausal levels by transdermal estradiol administration suppressed skeletal sympathetic activity [45]. This effect was attributed to a direct estradiol effect on cen-

tral nervous autonomic centers which could also explain the sex-specific differences in sympathetic outflow to the muscle vascular bed [45]. Since lack of estrogens also induces a central visceral fat accumulation, further work is required to assess direct influences of estrogen deficiency versus indirect effects mediated by visceral fat accumulation (Figure 2).

Visceral Obesity and Psychosocial Stress

Although intraabdominal visceral fat is associated with an increase in energy intake, this is not an absolute requirement [44]. Thus, additional factors appear to promote visceral obesity. It has been proposed that visceral obesity can be associated with hypothalamic-pituitary dysregulation and sympathetic activation [3]. There is also evidence that in obese persons, a dysregulated hypothalamic-pituitary axis could contribute to the raised basal MSNA [13]. This suggests that psychosocial loads promoting visceral obesity can amplify sympathetic overactivity.

Even in the absence of visceral obesity, there is strong evidence in favor of a crucial influence of psychosocial loads on cardiovascular mortality and morbidity. Of particular interest became the "effort-reward imbalance" model of Siegrist et al. [4, 24, 36]. The focus of this model is on occupational life where high-cost/low-gain conditions are considered particularly stressful. Variables measuring low reward in terms of low status control (e.g., lack of promotion prospects, job insecurity) in association with high extrinsic (e.g., work pressure) or intrinsic (personal coping pattern, e.g., high need for control) effort independently predicted new cardiovascular events. It remains an intriguing hypothesis that certain psychosocial loads not only reinforce an unfavorable dietary profile but also promote visceral fat deposition. Furthermore, unfavorable stress-induced molecular events such as a depressed Ca^{2+} transport activity of the sarcoplasmic reticulum need further investigations [32].

Sympathetic System and Vascular Remodeling

Sympathetic overactivity leads to peripheral vasoconstriction, increased heart rate and is also expected to raise renin release and to amplify angiotensin (AT) II formation. AT II promotes not only norepinephrine release from sympathetic nerve endings [7] but stimulates autonomous centers in the brain which further raise sympathetic outflow [34]. In addition, AT II stimulates the production of aldosterone which causes sodium retention. An increased sodium level increases the reactivity of smooth muscle and also enhances sympathetic nervous
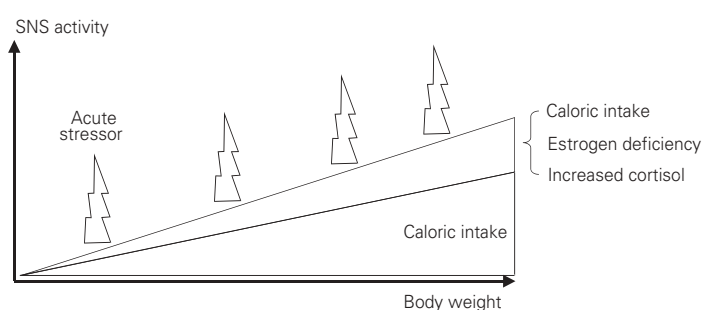

Figure 2. Schematic representation of determinants of sympathetic nervous system (SNS) activity related to calorie intake, estrogen deficiency, increased cortisol level, and stressors.
Abbildung 2. Schematische Darstellung zum Einfluss von Kalorienaufnahme, Östrogenmangel, erhöhtem Cortisol und Stressoren auf die Sympathikus-(SNS-)Aktivität.

system activity. Thus, several reenforcing mechanisms originating from sympathetic overactivity exist which favor the manifestation of hypertension. A hallmark of cardiovascular disorders is an adverse remodeling of the extracellular matrix of the vasculature involving an increased collagen deposition. Remodeling of arterioles is detected early because of an increased systolic and diastolic blood pressure. If the adverse influences persist, also the adverse remodeling of conduit arteries, which store blood during systole, becomes apparent. Due to the reduced capacitive function of large arteries and the aorta, the diastolic blood pressure "normalizes", while systolic blood pressure becomes high, i.e., systolic hypertension. In addition to collagen accumulation, calcification and atherosclerotic lesions occur.

A recent meta-analysis evaluating the risks of treated and untreated systolic hypertension showed that at any given level of systolic blood pressure, the risk of death rose with lower diastolic blood pressure and, therefore, also with greater pulse pressure [38]. This is not unexpected, since a reduced diastolic blood pressure impairs coronary perfusion and thus leads to a further depression of heart function.

In view of the deleterious consequences of an adverse remodeling of large arteries, efforts should be made to identify initiating pathophysiologic processes for achieving a more rational drug treatment. A major factor contributing to collagen deposition is AT II. We have shown that collagen type I mRNA and collagen synthesis of cultured fibroblasts is markedly stimulated by AT II which was prevented by an angiotensin receptor (AT I) blocker [5]. It was concluded that drugs counteracting AT II should have particular benefits on age-related vascular damage [16].

AT II is generated, however, not only from AT I by the angiotensin-converting enzyme (ACE) but also from other peptidases such as chymase [2, 15]. Chymase, which originates from mast cells, is the major AT II-forming enzyme in human heart and aorta in vitro. While chymase is not involved in functional regulation of blood pressure, evidence is accumulating that it may be involved in structural remodeling of the cardiovascular system. It appears that local AT II formation is increased in atherosclerotic lesions and that chymase is primarily responsible for this increase. Thus, it can be speculated that interventions that interfere with atherosclerotic processes could also counteract large artery remodeling by reducing influences from chymase. It is of interest in this respect that in elderly women aged 60–85 years, the localization of fat mass was more important for atherosclerosis than obesity per se. Central fat mass was associated with atherogenic tendencies, the peripheral fat mass seemed to exhibit even an independent dominant antiatherogenic effect [41]. Since the AT II production by chymase cannot be prevented by ACE inhibitors, AT I receptor blockers would be required for inhibiting excess AT II influences. Preferred would be AT I blockers which have an inhibitory action on presynaptic norepinephrine release [7, 30].

Abdominal Fat and the Metabolic Syndrome

Reduction of high arterial blood pressure is associated with a lower cardiovascular morbidity and mortality. It remains, however, intriguing that the mortality of hypertensives with apparently well-controlled blood pressure is higher than in normotensive persons. The question arises, therefore, whether a solely blood pressure-oriented therapy is adequate. Increasing evidence indicates that high blood pressure represents a chronic and slowly progressing disease and should be regarded as a symptom of an underlying complex disorder which is often associated with sympathetic overactivity.

A major factor contributing to cardiovascular morbidity and mortality is insulin resistance and other disorders of the metabolic syndrome. Although many studies have shown an association between intraabdominal fat accumulation and insulin resistance, possible causal mechanisms remain ill-defined. Abdominal fat differs in various crucial parameters from subcutaneous fat. Visceral fat is characterized by a high metabolic and lipolytic rate [44] leading to an enhanced release of fatty acids into the portal vein. Increased levels of fatty acids would be expected to favor insulin resistance by a number of

mechanisms particularly involving the "Randle cycle" [26]. It has, however, been argued that the lipolysis would have to be balanced with a correspondingly high fat storage [10]. It has been suggested that the often more abundant subcutaneous abdominal fat has a major influence on plasma free fatty acids [10].

An increased sympathetic activity can reinforce insulin resistance involving several mechanisms. The glucose output of the liver is increased, while insulin secretion of the pancreatic β-cells becomes diminished. This mechanism guarantees the supply of glucose for the insulin-independent glucose utilization by the brain under conditions of food shortage. The lipolysis-induced increase in plasma fatty acids causes, at the same time, a further reduction in peripheral glucose utilization. Chronic modifications in the morphology of skeletal muscle contribute to a further reduction in insulin sensitivity. A reduction of the capillary density occurs [20], i.e., rarefaction that is associated with increased diffusion distances for oxygen and probably also glucose. Although the ensuing hyperinsulinemia can initially prevent the occurrence of hyperglycemia, this state can frequently not be maintained and leads to established type 2 diabetes.

Conclusion

Sympathetic overactivity arising from calorie intake-dependent and -independent mechanisms has a crucial role in triggering a number of adverse reactions which can lead to hypertension and metabolic disorders. The present focus on visceral fat accumulation strengthens the concept of an "excess catecholamine syndrome" of which the now well-accepted "metabolic syndrome" appears as one consequence.

References

1. Alvarez GE, Beske SD, Ballard TP, et al. Sympathetic neural activation in visceral obesity. Circulation 2002;106:2533–6.
2. Arakawa K, Urata H. Hypothesis regarding the pathophysiological role of alternative pathways of angiotensin II formation in atherosclerosis. Hypertension 2000;36:638–41.
3. Bjorntorp P. Do stress reactions cause abdominal obesity and comorbidities? Obes Rev 2001;2:73–86.
4. Bosma H, Peter R, Siegrist J. Two alternative job stress models and the risk of coronary heart disease. Am J Public Health 1998;88:68–74.
5. Brilla CG, Scheer C, Rupp H. Renin-angiotensin system and myocardial collagen matrix: modulation of cardiac fibroblast function by angiotensin II type 1 receptor antagonism. J Hypertens Suppl 1997;15:S13–9.
6. Eikelis N, Schlaich M, Aggarwal A, et al. Interactions between leptin and the human sympathetic nervous system. Hypertension 2003;41:1072–9.

7. Esler M. Differentiation in the effects of the angiotensin II receptor blocker class on autonomic function. J Hypertens 2002;20: Suppl 5:S13–9.

8. Esler M, Lambert G, Brunner-La Rocca HP, et al. Sympathetic nerve activity and neurotransmitter release in humans: translation from pathophysiology into clinical practice. Acta Physiol Scand 2003;177:275–84.

9. Esler M, Rumantir M, Wiesner G, et al. Sympathetic nervous system and insulin resistance: from obesity to diabetes. Am J Hypertens 2001;14:304S–9S.

10. Frayn KN. Visceral fat and insulin resistance – causative or correlative? Br J Nutr 2000;83:Suppl 1:S71–7.

11. Grassi G, Seravalle G, Cattaneo BM, et al. Sympathetic activation in obese normotensive subjects. Hypertension 1995;25:560–3.

12. Grassi G, Seravalle G, Colombo M, et al. Body weight reduction, sympathetic nerve traffic, and arterial baroreflex in obese normotensive humans. Circulation 1998;97:2037–42.

13. Grassi G, Seravalle G, Dell'Oro R, et al. Participation of the hypothalamus-hypophysis axis in the sympathetic activation of human obesity. Hypertension 2001;38:1316–20.

14. Iacobellis G, Assael F, Ribaudo MC, et al. Epicardial fat from echocardiography: a new method for visceral adipose tissue prediction. Obes Res 2003;11:304–10.

15. Ihara M, Urata H, Kinoshita A, et al. Increased chymase-dependent angiotensin II formation in human atherosclerotic aorta. Hypertension 1999;33:1399–405.

16. Izzo JL Jr. Systolic hypertension, arterial stiffness, and vascular damage: role of the renin-angiotensin system. Blood Press Monit 2000;5:Suppl 2:S7–11.

17. Jones PP, Snitker S, Skinner JS, et al. Gender differences in muscle sympathetic nerve activity: effect of body fat distribution. Am J Physiol 1996;270:E363–6.

18. Julius S, Pascual AV, Sannerstedt R, et al. Relationship between cardiac output and peripheral resistance in borderline hypertension. Circulation 1971;43:382–90.

19. Ley CJ, Lees B, Stevenson JC. Sex- and menopause-associated changes in body-fat distribution. Am J Clin Nutr 1992;55:950–4.

20. Lind L, Lithell H. Decreased peripheral blood flow in the pathogenesis of the metabolic syndrome comprising hypertension, hyperlipidemia, and hyperinsulinemia. Am Heart J 1993;125:1494–7.

21. Lissner L, Bjorkelund C, Heitmann BL, et al. Larger hip circumference independently predicts health and longevity in a Swedish female cohort. Obes Res 2001;9:644–6.

22. Muller MJ, Bosy-Westphal A, Kutzner D, et al. Metabolically active components of fat-free mass and resting energy expenditure in humans: recent lessons from imaging technologies. Obes Rev 2002;3:113–22.

23. Pasquali R, Casimirri F, Labate AM, et al. Body weight, fat distribution and the menopausal status in women. The VMH Collaborative Group. Int J Obes Relat Metab Disord 1994;18:614–21.

24. Peter R, Siegrist J. Chronic work stress, sickness absence, and hypertension in middle managers: general or specific sociological explanations? Soc Sci Med 1997;45:1111–20.

25. Poehlman ET, Toth MJ, Gardner AW. Changes in energy balance and body composition at menopause: a controlled longitudinal study. Ann Intern Med 1995;123:673–5.

26. Randle PJ. Regulatory interactions between lipids and carbohydrates: the glucose fatty acid cycle after 35 years. Diabetes Metab Rev 1998;14:263–83.

27. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595–607.

28. Rupp H. Excess catecholamine syndrome. Pathophysiology and therapy. Ann N Y Acad Sci 1999;881:430–44.

29. Rupp H, Jacob R. Excess catecholamines and the metabolic syndrome: should central imidazoline receptors be a therapeutic target? Med Hypotheses 1995;44:217–25.

30. Rupp H, Jaeger B. The renin-angiotensin system and the sympathetic nervous system in hypertension and congestive heart failure: implications for therapeutic interventions. J Clin Basic Cardiol 2001;4:47–51.

31. Rupp H, Maisch B. Radiotelemetric characterization of overweight-associated rises in blood pressure and heart rate. Am J Physiol 1999;277:H1540–5.

32. Rupp H, Maisch B, Brilla CG. Schedule-induced psychological stress and molecular structures of cardiomyocytes. Am J Physiol 1997;272:R776–82.

33. Scherrer U, Randin D, Tappy L, et al. Body fat and sympathetic nerve activity in healthy subjects. Circulation 1994;89:2634–40.

34. Scholkens BA, Jung W, Rascher W, et al. Brain angiotensin II stimulates release of pituitary hormones, plasma catecholamines and increases blood pressure in dogs. Clin Sci 1980;59:Suppl 6:53s–6s.

35. Seidell JC, Perusse L, Despres JP, et al. Waist and hip circumferences have independent and opposite effects on cardiovascular disease risk factors: the Quebec Family Study. Am J Clin Nutr 2001;74:315–21.

36. Siegrist J, Klein D, Voigt KH. Linking sociological with physiological data: the model of effort-reward imbalance at work. Acta Physiol Scand Suppl 1997;640:112–6.

37. Snijder MB, Dekker JM, Visser M, et al. Associations of hip and thigh circumferences independent of waist circumference with the incidence of type 2 diabetes: the Hoorn Study. Am J Clin Nutr 2003;77:1192–7.

38. Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. Lancet 2000;355:865–72.

39. Sumino H, Ichikawa S, Yoshida A, et al. Effects of hormone replacement therapy on weight, abdominal fat distribution, and lipid levels in Japanese postmenopausal women. Int J Obes Relat Metab Disord 2003;27:1044–51.

40. Taguchi R, Takasu J, Itani Y, et al. Pericardial fat accumulation in men as a risk factor for coronary artery disease. Atherosclerosis 2001;157:203–9.

41. Tanko LB, Bagger YZ, Alexandersen P, et al. Peripheral adiposity exhibits an independent dominant antiatherogenic effect in elderly women. Circulation 2003;107:1626–31.

42. Toth MJ, Tchernof A, Sites CK, et al. Effect of menopausal status on body composition and abdominal fat distribution. Int J Obes Relat Metab Disord 2000;24:226–31.

43. Vaz M, Jennings G, Turner A, et al. Regional sympathetic nervous activity and oxygen consumption in obese normotensive human subjects. Circulation 1997;96:3423–9.

44. Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. Endocr Rev 2000;21:697–738.

45. Weitz G, Elam M, Born J, et al. Postmenopausal estrogen administration suppresses muscle sympathetic nerve activity. J Clin Endocrinol Metab 2001;86:344–8.

Address for Correspondence
Prof. Heinz Rupp, PhD
Molecular Cardiology Laboratory
Department of Internal Medicine and Cardiology
Philipps University Marburg
Karl-von-Frisch-Straße 1
35033 Marburg
Germany
Phone (+49/6421) 286-5032, Fax -8964
e-mail: Rupp@staff.uni-marburg.de