DOWNLOAD PDF INVOLVEMENT OF LEPTIN IN ARTERIAL HYPERTENSION JERZY BELTOWSKI

Chapter 1 : Jerzy Beltowski

arterial hypertension, leptin, leptin resistance, Na+,K+-ATPase, natriuresis, nitric oxide, oxidative stress Search for Similar Articles You may search for similar articles that contain these same keywords or you may modify the keyword list to augment your search.

Article ABSTRACT This novel study was designed to evaluate the possible effects of topically formulated melatonin cream alone or in combination with sunscreen and oral melatonin for the management of melasma patients in comparison with hydroquinone as a standard therapy. This study carried out in the dermatology department at the AL-Karama teaching hospital, Baghdad, Iraq. In a double blind manner, this preliminary clinical study was performed on 36 patients with epidermal melasma and 10 healthy subjects as control. They were diagnosed as having melasma and they were under dermatologist supervision during the entire period of treatment. To evaluate the oxidative stress status, malondialdehyde MDA and glutathione GSH levels in plasma were measured before starting treatment and after 45, 90, and days of treatment. At the end of treatment period 90 days ; all melasma patients demonstrated significant reduction in MASI score in different levels. In addition, the plasma MDA levels were decreased and plasma GSH levels were increased in different scales after 90 days of treatment. The overall results of this preliminary study suggested that topical melatonin could be used as a hypopigmenting agent in treatment of melasma, and this effect is augmented by the oral administration of the drug and the use of sunscreen, possibly by its antioxidant activity or by other mechanisms unrelated to antioxidant effect. Oxidative stress, melatonin level, and sleep insufficiency among electronic equipment repairers. Exposure to extremely low frequency electromagnetic field ELF-EMF , especially among electronic equipment repairers may induce oxidative stress and affect sleep quality. Effect of melatonin on spinal cord injury induced lipid peroxidation in rats: In the present study, we determine the effects of melatonin as an antioxidant on the whole blood indices stored Therapeutic potential of the epidermal growth factor receptor transactivation in hypertension: However, it is unclear how and why such apparently distinct processes coincide in hypertension. Role in the Pathogenesis of Arterial Hypertension. Plasma leptin concentration is increased in obese individuals. Chronic leptin administration or transgenic overexpression increases blood pressure in experimental Methods and results Accelerated atherosclerotic lesions were established by administration of a high-fat diet However, very little is known about the effects of ozone exposure on human skin. Here, contributions of redox cycling and alkylating properties of quinones both natural and synthetic, such as plumbagin, juglone, lawsone, menadione, methoxy-naphthoquinones, and others to

Chapter 2 : Leptin and Hypertension in Obesity

Here, current knowledge about the role of leptin in the regulation of blood pressure and in the pathogenesis of arterial hypertension is presented. Read more Article.

Received Sep 27; Accepted Dec This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. This article has been cited by other articles in PMC. Abstract Leptin is a kDa-peptide hormone that is primarily synthesized and secreted by adipose tissue. One of the major actions of this hormone is the control of energy balance by binding to receptors in the hypothalamus, leading to reduction in food intake and elevation in temperature and energy expenditure. In addition, increasing evidence suggests that leptin, through both direct and indirect mechanisms, may play an important role in cardiovascular and renal regulation. While the relevance of endogenous leptin needs further clarification, it appears to function as a pressure and volume-regulating factor under conditions of health. However, in abnormal situations characterized by chronic hyperleptinemia such as obesity, it may function pathophysiologically for the development of hypertension and possibly also for direct renal, vascular, and cardiac damage. Introduction The prevalence of obesity in the adult population of the United States has risen markedly in the last three decades, contributing to the increased incidence of diabetes, hypertension, and heart disease [1 â€” 3]. Recently, a novel and most promising area of research in obesity and hypertension that links these two pathologic conditions is the endocrinology of adipose tissue. It is now apparent that adipose tissue is a prolific organ which secretes several immunomodulators and bioactive molecules [3 , 6]. Of these various factors, leptin has emerged as an important hormone with significant pleiotropic actions on several organ systems [7 , 8]. The first described major action of leptin was on the hypothalamus to control body weight and fat deposition through its effects on appetite inhibition, as well as stimulation of the metabolic rate and thermogenesis [9 , 10]. However, increasing evidence suggests that the biology of leptin extends to other organs including the kidney, the heart, the sympathetic nervous system, and the systemic vasculature, areas in which it may have prominent effects [7 , 8 , 11 â€” 14]. Localization and Function The leptin receptor LR , a product of the lepr gene, is a member of the extended class I cytokine receptor family having at least six splice variants LR a-f [15 â€” 19]. Significant expression of the lepr gene occurs in the lung and adipocytes, while only moderate levels appear in the kidney, with relatively lower levels demonstrated in other tissues like the heart, brain, spleen, liver, and muscle [20]. Though the extracellular domain of the leptin receptor and the short splice variant LRa have been detected in many peripheral tissues, the long splice variant LRb is expressed in fewer organ systems including the adrenal gland, kidney, and heart [20]. This long splice variant leads to activation of the Janus Kinases a family of tyrosine kinases to promote transcription through activation of the STAT-3 signal transduction and activator of transcription and PI3K phosphoinositol-3 kinase , and inhibition of AMPK AMP-activated protein kinase [15 â€” 20]. Finally, SOCS-3 suppression of cytokine signaling protein and PTB1b protein tyrosine phosphatase 1b have been identified as negative regulators of leptin signaling [15 â€” 19]. Leptin, Sympathetic Nervous System, and the Regulation of Arterial Blood Pressure It is now well established that leptin can activate the sympathetic nervous system both by local peripheral actions as well as through centrally mediated effects on the hypothalamus [22]. Moreover, recent investigations have suggested that leptin signaling in the nucleus tracti solitarii increased renal sympathetic flow in normal rats but not in obese Zucker rats, indicating that intact leptin receptors are essential for this vasoactive response [22]. In agreement with these concepts, human studies have suggested that genetically mediated leptin deficiency is associated not only with morbid obesity, but also impairment in the sympathetic nervous system activity and postural hypotension in homozygous children and adults [23]. However, it is important to point out that in other investigations conducted both in normotensive as well as hypertensive rats [12 , 14 , 24], the acute systemic administration of leptin was associated with the peripheral

activation of the sympathetic nervous system without elevation in MAP. This raises the possibility of the simultaneous local activation of counter-regulatory vasodilatory mechanisms [14 , 25 , 26]. In vitro studies have demonstrated a dose-dependent leptin-induced vasorelaxation in the aortic rings of Wistar-Kyoto rats [25] which is mediated by nitric oxide NO and possibly by endothelial-derived hyperpolarizing factor EDHF. An elevation in plasma NO with intravenous administration of synthetic leptin in normal rats has also been demonstrated [26]. In these studies blockade of NO led to a leptin-induced enhancement of arterial blood pressure while blockade of the sympathetic nervous system led to leptin-mediated reduction in blood pressure [26]. This concept requires further validation because the vasodilatory actions of leptin in other vascular beds have been found to be inconsistent [28 , 29]. In high-calorie fed obese rats, however, recent studies by Beltowski et al have indicated that acutely infused leptin was associated with a hypertensive effect related, at least in part, to impaired vascular NO and EDHF production characteristic of obesity [30]. Chronic Hyperleptinemia, Leptin Resistance, and Hypertension In chronic hyperleptinemic conditions such as obesity, the potential neutral effect of leptin on peripheral vascular resistance may no longer be present. It has been previously demonstrated that the agouti yellow obese mouse model is resistant to the satiety actions of leptin but not to the effects of leptin on the sympathetic nervous system [31 , 32], although this stimulation may be attenuated with the progression of obesity [33]. The precise factors behind this selectivity are yet to be fully defined [32 , 34], but may involve alterations in the SOCS3 signaling pathway or IRS-1 insulin receptor substrate-1 serine residue phosphorylation [30 , 35 , 36]. Independent of the possibility of selective leptin resistance in obesity, studies in normal rats have demonstrated that chronic hyperleptinemia leads to a persistent elevation in MAP and this hypertensive effect is rapidly reversed upon cessation of the hormone administration [37]. Similar increases in systolic blood pressure have been demonstrated in transgenic mice overexpressing leptin where the endogenous level of the hormone was elevated twenty-fold [38]. In humans, emerging evidence suggests a direct relationship between hyperleptinemia and hypertension in both men and women [39 , 40], and this effect may be independent of BMI and insulin resistance. In this regard, recent studies indicating a reduction in serum leptin levels with the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers suggest a potential interaction between leptin and the renin-angiotensin-aldosterone system for hemodynamic regulation in obesity [42 , 43]. To this end, Greenfield et al. Leptin and the Regulation of Sodium-Volume Balance Previous studies have indicated that the LRb leptin receptor is localized in the renal medulla [20 , 47] which suggests a functional role of this hormone in renal biology. In the last 5â€”10 years, numerous studies have demonstrated that acute administration of synthetic leptin in the rat produces a significant elevation in urinary sodium and water excretion [14 , 47 â€” 49]. Interestingly, the natriuretic effect was attenuated in obese Zucker rats [14]. MAP and creatinine clearance remained unchanged in all of the rat strains with the acute infusion of the hormone. Collectively, these findings were interpreted to suggest that leptin might be a natriuretic hormone primarily acting at the tubular level for promotion of sodium and water excretion in normal rats, and that leptin may function pathophysiologically in obesity and hypertension, where chronic hyperleptinemia may contribute to a preferential stimulation of the sympathetic nervous system with further elevation in blood pressure and reduced sodium and water excretion [2 , 7 , 50]. Moreover, in a rat model of diet-induced obesity, initial studies by Patel et al. However, additional observations in diet-induced obese rats indicate that caloric restriction was associated with the restoration of the natriuretic actions of leptin as well as with the renal generation of NO [51]. In the aggregate, these studies are consistent with the concept that obesity is associated with renal leptin resistance [14 , 52], and this resistance, at least in part, is reversible with caloric restriction and weight loss. The significance of NO in the direct modulation of leptin-induced sodium excretion has been investigated in rats chronically treated with L-NAME to inhibit NO production [53]. L-NAME-treated rats failed to produce significant natriuresis. However, there was a two to threefold elevation in sodium excretion induced by leptin with the restoration of NO by sodium nitroprusside [53], indicating that NO may play an important role in mediating or modulating the tubular natriuretic effects of leptin. These

observations are supported by the studies of Beltowski et al. The mechanisms for renal resistance to leptin in obesity and hypertension are not completely defined but may include receptor down regulation [12 , 51], postreceptor signaling alterations [12 , 16 , 17], excessive degradation of NO produced by oxidative stress [55], or increased activation of the efferent renal sympathetic nervous system leading to antinatriuresis [49]. Indeed, studies which [49] have examined this latter hypothesis using an animal model of renal denervation indicate that the renal efferent sympathetic nervous system is an important counter-regulatory mechanism impeding leptin-induced sodium excretion in hypertension, and perhaps also during obesity, which is similarly characterized by a heightened sympathetic nervous tone [2 , 7]. The importance of leptin as a regulator of sodium and volume is further supported by recent investigations [56 , 57] which have demonstrated that leptin expression in adipose tissue is directly proportional to dietary sodium, a response that would be expected for mechanisms regulating sodium balance. The responsiveness to leptin at neural, renal, and other sites which regulate natriuresis and vascular resistance may differ under diverse physiological and pathophysiological conditions, and this in turn, will be a determinant for the overall magnitude of leptin-induced sodium, water, and hemodynamic balance. As previously discussed, leptin may play a significant role in the regulation of sodium and water balance in normal situations. However, in conditions of chronic hyperleptinemia, the hormone has been linked to renal structural changes that specifically have been associated with obesity [58]. Elegant studies by Wolf et al. Indeed, chronic infusion of leptin in normal rats promoted the development of glomerulosclerosis and proteinuria [59]. It is of interest that similar renal abnormalities have been found in mice with chronic high fat diet and the metabolic syndrome [60], which is characterized by sustained elevations of circulating leptin [61]. Inappropriate elevation in serum leptin levels has been demonstrated in patients with chronic kidney disease [62 â€” 64]. The origin and significance of hyperleptinemia in these patients are not completely defined, but it is important to emphasize that the marked elevation of leptin is out of proportion to obesity and persists after correction for body mass index [65]. Since the kidney is involved in clearance of leptin, its elevated levels in renal insufficiency are primarily due to reduced renal filtration and metabolism [62 , 66]. It remains to be determined whether an increased rate of leptin production also contributes to the high serum leptin levels in renal insufficiency. Leptin levels appear to be higher in patients receiving peritoneal dialysis PD compared to hemodialysis HD [67]. The reasons for this phenomenon are multifactorial. It is likely that the elevated body fat mass in patients with PD contributes to the increase in serum leptin [67]. However, other factors are probably involved. For instance, the continuous glucose load in PD results in chronic hyperinsulinemia, an important finding considering that insulin upregulates lepr gene expression [63]. In this regard, it is of interest that even higher leptin levels are observed in patients with renal insufficiency with elevated insulin levels compared to patients with low insulin levels [63 , 68]. The pathophysiological significance of hyperleptinemia in renal insufficiency is not completely understood. High levels of leptin have been associated with weight loss in dialysis patients [65 , 69 â€” 71], and therefore it has been suggested that hyperleptinemia may be a contributing factor in uremic-induced cachexia [64 , 69 â€” 74]. Other suggested actions in patients with end-stage renal disease which include leptin-induced reduction in erythropoiesis [75 , 76], promotion of renal osteodystrophy [77 , 78], and chronic inflammation [63 , 78 , 79]. Leptin and the Heart It is now well recognized that the role of leptin in energy homeostasis extends into cardiac metabolism. The effects of leptin mediated by the LRb receptor include a reduction of insulin signaling with enhanced lipid oxidation and therefore inhibition of anabolic pathways [80]. Similar to the kidney, chronic hyperleptinemia may be indirectly important in the development of cardiac disease via sympathetic activation, pressor effects, enhancement of platelet aggregation, impairment of fibrinolysis as well as proangiogenic actions [12 , 35 , 81 , 82] and systemic inflammation via leptin-induced expression of C-reactive protein [83 , 84]. In addition, and although still controversial, leptin may be involved in the pathogenesis of myocyte hypertrophy and cardiac dysfunction [85 â€” 87] through direct effects. Indeed, leptin can proliferate, differentiate, and functionally activate hemopoietic and embryonic cells to promote myocyte growth [88 â€” 90]. Moreover, in rats with myocardial

infarction, cardiac hypertrophy has been shown to be attenuated with the blockade of leptin receptors [91]. Among the suggested mechanisms of leptin-induced hypertrophy are the stimulation of endothelin-1, angiotensin II [92], and reactive oxygen species [93]. Additional studies in rats with myocardial infarction have also indicated that long-term continuous administration of leptin promoted the development of eccentric cardiac hypertrophy [94]. Also, Tajmir et al. Presently, the reasons for the apparent discrepant effects of leptin on myocyte growth are unclear, but may be related to different experimental conditions, including the variable response of leptin in neonatal compared to adult cells [82 â€” 97]. In addition to its potential actions on myocardial cell growth, leptin has been shown to exert direct negative inotropic effects on adult rat ventricular myocytes [98]. The suggested mechanisms involve activation of fatty acid oxidation leading to decreased triglyceride content or an altered adenylate cyclase function [96 , 99]. Alternatively, Nickola et al. The relevance of these studies in humans is unclear. Although there is evidence to suggest a direct relationship between the hyperleptinemia of obesity with cardiac hypertrophy [96 ,], and possibly heart failure [ ], these are not consistent findings [8 , 11]. Additional in vitro and in vivo studies are needed to define and characterize the potential beneficial or deleterious effects of leptin in cardiac physiology and pathophysiology. Summary and Conclusions It is well established that cardiovascular and renal functions require the activation of multiple neuro hormonal mechanisms designed to maintain homeostasis. The hormone leptin has multiple actions that may be important not only for energy metabolism, but also in physiological and pathophysiological cardiovascular and renal regulation Figure 1. Potentially prominent are its effects on renal sodium excretion, NO, sympathetic nervous system activation, and vascular tone. The interaction among the vasoconstricting, vasodilatory, and natriuretic effects of leptin to help achieve volume and pressure homeostasis in normal conditions may be disrupted during chronic hyperleptinemia, and this effect could likely contribute to hypertension and possible cardiac and renal dysfunction. Further research awaits the additional characterization of both direct and indirect mechanisms of action of leptin, including its interface with other important hormonal sodium-volume-pressure regulatory systems, in both health and disease states, particularly obesity and related comorbidities.

Chapter 3 : The Role of Leptin in Obesity-Induced Hypertension | Texila International Journal - calendrierde

Leptin is a kDa peptide hormone that is primarily synthesized and secreted by adipose tissue. One of the major actions of this hormone is the control of energy balance by binding to receptors in the hypothalamus, leading to reduction in food intake, elevation in temperature and energy expenditure. in addition, increasing evidence suggests that leptin, through both direct and indirect.

Leptin, a peptide discovered more than 10 years ago, decreases food intake and Stephen Morse 1 increases sympathetic nerve activity to both thermogenic and nonthermogenic tissue. Leptin David M Borne 2 was initially believed to be an anti-obesity hormone, owing to its metabolic effects. However, Erwin A Aguilar 1 obese individuals, for unknown reasons, become resistant to the satiety and weight-reducing effect of the hormone, but preserve leptin-mediated sympathetic activation to nonthermogenic Efrain Reisin 1 tissue such as kidney, heart, and adrenal glands. Leptin has been shown to influence nitric 1 Sections of Nephrology and oxide production and natriuresis, and along with chronic sympathetic activation, especially 2 Comprehensive Medicine, Department of Internal Medicine, to the kidney, it may lead to sodium retention, systemic vasoconstriction, and blood pressure Louisiana State University Health elevation. Consequently, leptin is currently considered to play an important role in the Sciences Center, New Orleans, LA, development of hypertension in obesity. Hence, hypertension in obesity has become a topic of extensive ongoing research. Now, several mechanisms have been implicated in the association between obesity and hypertension, including activation of sympathetic nervous system, abnormal renal sodium handling, insulin resistance, and physical compression of the kidney Haynes et al In this respect, sympathetic activation appears to mediate at least part of the obesity-induced hypertension, and leptin, the adipocyte-derived hormone, has recently been postulated as one of the possible causes of this sympathetic activation in obesity. Leptin is a amino acid hormone discovered in that is almost exclusively produced by adipose tissue and possibly secreted by a constitutive mechanism. The effects of this peptide are mediated by receptors Ob-R , most of them located in the hypothalamus, belonging to the class l cytokine receptor family. As of yet, 6 leptin receptor isoforms are known Ahima and Flier Efrain Reisin Chief of the Section of Nephrology, Leptin is considered a homeostatic hormone regulating food intake and body Department of Internal Medicine, weight. Acting on the hypothalamic nuclei, leptin decreases appetite, and increases Louisiana State University Health Sciences Center Tulane Avenue, energy expenditure through sympathetic activation, which consequently decreases New Orleans, LA , USA adipose tissue mass and body weight. Due to latter homeostatic control mechanism, leptin is an anti- Vascular Health and Risk Management All rights reserved Bravo et al obesity hormone, based on the hypothetical fact that high resistance is due to an impaired leptin transport mechanism leptin levels would prevent the occurrence of obesity. Moreover, the increased RSNA found in obese individuals now suggests the existence of achieved by central leptin administration was not an endogenous leptin-resistant mechanism in obesity accompanied by changes in plasma leptin levels, suggesting Considine et al In addition to regulating food intake and adipose tissue In agreement with these observations, Munzberg et al mass, leptin has been found to be involved in cardiovascular recently described that leptin resistance is not global physiological processes like sympathetic nerve system within the hypothalamus, and found that the arcuate nuclei, activation, renal hemodynamics, blood vessel tone, and which contains leptin-mediated anorexigenic neurons, blood pressure. This review will focus on the leptin-mediated becomes resistant to leptin in very early stages of diet- sympathetic activation and its relevance to the mechanism induced obesity in mice. On the contrary, other hypothalamic of obesity-related hypertension. As stated above, obesity is associated with high leptin levels, This hypothesis, however, must be proved in human reflecting the increased amount of adipose tissue in obese studies as well, and if true, it would help explain how leptin individuals. As a consequence, it has been postulated that could contribute to sympathetic activation and hypertension the apparent loss of the anorexic and weight-reducing effects despite the fact that there is resistance to the satiety and of leptin in

obesity, is a result of a leptin-resistance weight-reducing effects of leptin in obesity. Nevertheless, obesity is associated with increased sympathetic nerve activity, and leptin has been Renal effects of leptin: Therefore, it is contradictory that, in the presence and nitric oxide of a leptin resistance state, the hormone can contribute to In the kidney, leptin may affect blood pressure mainly by the sympathetic activation seen in obesity. This has led to two opposing ways: This concept has to the hormone. As it has been observed, acutely emerged from observations made first in agouti yellow obese administered leptin usually does not increase blood pressure Ay mice Correia et al ; Rahmouni et al , and in animal or human studies, but when given for longer corroborated recently in a diet-induced obesity model periods of time, leptin does elevate blood pressure in animal Rahmouni et al In these studies, leptin administered models. Interestingly, this same effect was observed activation has been thought to contribute to the when leptin was injected into the lateral ventricle of the development of hypertension by enhancing sodium brain Rahmouni et al , Here, leptin increased retention, since renal denervation attenuates the RSNA again, without changing significantly food intake and antinatriuretic and hypertensive effect of obesity in dogs body weight in Ay and diet-induced obese mice, as compared Kassab et al Although systemic administration with their respective lean littermates. These latter studies of leptin stimulates sympathetic nerve activity to the also served to demonstrate that is unlikely that leptin kidney Haynes, Morgan, et al , if infused for short Vascular Health and Risk Management The increased natriuresis Conversely, long-term leptin administration increases both and fractional sodium excretion are not accompanied by RSNA and blood pressure. Recent data indicate that chronic substantial changes in glomerular filtration rate or the hyperleptinemia decreases natriuresis and urinary excretion reninâ€”aldosterone axis suggesting a decreased sodium of NO metabolites NOx Beltowski, Jamroz-Wisniewska, tubular transport. Beltowski, Wojcicka, et al et al Apparently, long-term leptin administration. New evidence suggests that leptin hyperleptinemic states like obesity increase the level of stimulates systemic NO release which opposes the pressor systemic and intrarenal oxidative stress, leading to NO and antinatriuretic effect of leptin-induced sympathetic deficiency Beltowski, Wojcicka, et al Leptin, activation Beltowski, Wojcicka, Borkowska, et al ; chronically, would reduce natriuresis by up-regulation of Beltowski, Jochem, et al In other Wisniewska, et al Ortiz and Garvin Likewise, Villarreal et al Supporting these observations, Bickel et al found that chronic inhibition of NO synthesis impairs the reported an increased number of different sodium tubular acute leptin-mediated natriuretic effect in normotensive lean transporters in the kidney of obese rats. The kidney has been shown to express high amounts exhibited a decreased natriuretic effect after a saline load of leptin receptors Serradeil-Le Gal et al , yet it is when compared with their lean age mates. Interestingly, the short-term leptin-induced natriuretic Clinical relevance effect seen in lean animals was attenuated in obese rats and Chronic hyperleptinemia, as mentioned, augments the blood was even blunted in spontaneously hypertensive rats SHR pressure by means of different mechanisms in animal Villarreal et al ; Beltowski, Wojcicka, Gorny, et al models. In humans, there have been several studies This suggests a certain level of peripheral leptin attempting to link leptin to hypertension Figure 1. A number of studies have found leptin to be these states, such as an enhanced RSNA and reninâ€” positively correlated with systolic and diastolic blood angiotensin system Villarreal et al ; Beltowski, pressure in both obese Kunz et al ; Golan et al ; Wojcicka, Gorny, et al , which may have overcome Itoh et al ; Al-Hazimi and Syiamic ; Canatan et al leptin-mediated natriuresis. In agreement with this statement, a; Schutte et al and non-obese individuals Villarreal et al found that SHR after renal denervation Uckaya et al ; Adamczak et al ; Takizawa et al Vascular Health and Risk Management Adapted from Hall et al Am J Hypertension, 14 6 Pt 2: Al-Hazimi continued to correlate positively with mean arterial blood and Syiamic , for example, found that serum leptin pressure in the hypertensive, but not in the normotensive and angiotensin II levels were strong predictors of elevated obese group Itoh et al Interestingly, leptin has been blood pressure in obese women. Likewise, other found to be elevated in several hypertensive states of investigators Kunz et al ; Golan et al ; Canatan pregnancy as well Anato et al ; Vitoratos et al Of note is age and body mass index BMI. In another study leptin also the observation that a positive correlation between leptin correlated stronger with systolic and

diastolic blood pressure and platelet count levels exist in pre-eclamptic women than did with BMI or waist circumference in untreated Anato et al Moreover, one study found In disagreement to some of these data, one study found that after a 3-month weight reduction program, leptin that leptin levels were higher in hypertensives than in Vascular Health and Risk Management However this hypertension and eccentric-concentric left ventricular relationship between leptin and blood pressure may not hypertrophy: Although the studies are not yet consistent, it seems that pharmacologic suppression of the sympathetic nervous Possible treatment considerations system, the reninâ€”agiotensin system and, lately The elevated leptin concentrations seen in obese hypertensive hyperleptinemia with ACE inhibitors, ARB and BB, may humans are mainly due to abdominal adipose tissue secretion. Diuretics, on the other hand, by eliminating might be more relevant than others in terms of reducing leptin urinary sodium and extracellular fluid, might also play a levels in obesity. For example, angiotensin II has recently been significant role in the treatment of hypertension in obesity, found to stimulate leptin production in human adipose tissue as these individuals are known for being sodium retainers Skurk et al , possibly by means of activation of the and hypervolemics. Nevertheless, BBs and diuretics may angiotensin II type 1 receptor subtype. This effect was affect insulin sensitivity and cause hyperglycemia and so completely abolished when the angiotensin receptor blocker their use should be carried out with close monitoring of ARB candesartan was employed prior to angiotensin II glycemia in this patient population. In agreement with this observation, valsartan, another ARB, aside from lowering blood Summary pressure, decreased leptin levels and BMI in obese individuals, In summary, leptin the adipose tissue-derived hormone when compared with the calcium channel blocker CCB by way of distinct neurochemical pathways stimulates felodipine Fogari et al Similarly, the angiotensin- sympathetic nerve activity in thermogenic and converting enzyme ACE inhibitor, enalapril, in combination nonthermogenic tissue, affecting the metabolic and with a weight reduction program, evidenced the greatest cardiovascular system respectively. Leptin, acutely, could benefits in terms of weigh loss and diminution of plasma have a dual influence on blood pressure control, in which norepinephrine, insulin, and leptin levels in comparison with the net effect would depend on the balance between the control groups treated with weight reduction program alone or pressor action through activation of the sympathetic combined with the CCB amlodipine Masuo et al In nervous system and a possible natriuretic and peripheral another study, the beta-blocker BB pindolol showed a marked vasorelaxant effect of the hormone on the renal tubules suppressive effect on serum leptin levels, not seen in and endothelium. In contrast, chronic hyperleptinemia hypertensive individuals on perindopril, or felodipine Ficek may lead to abnormal renal sodium retention and et al Likewise, both enalapril and clonidine of the cardiovascular effect. Treatment of these reduced heart sympathetic activity and blood pressure in individuals might be focused in overcoming the another clinical trial, but failed to decrease serum leptin hemodynamic alterations seen in obesity, such as levels in normotensive obese and non-obese subjects after antinatriuresis and overactivity of the sympathetic and 7 days of treatment Amador et al Vascular Health and Risk Management Effects of obesity-hypertension on the heart. Adapted from Zhang et al Reproduced with permission from Zhang R, Reisin E. Am J Hypertens, Relationship between plasma of leptin-induced hypertension. Pol J Pharmacol, Influence of intravenously J Hum Hypertens, Ann Rev Physiol, Human leptin stimulates angiotensinII, leptin and arterial blood pressure. Saudi Med J, Leptin and heart oxide production, and renal sodium handling in leptin-induced sympathetic activity in normotensive obese and non-obese subjects. Ital Heart J, 5: Am J different types of hypertension during pregnancy. Plasma leptin and blood pressure plasma leptin levels in both genders of patients with essential in men: Relationship among levels Beach RE. Clin with essential hypertension and healthy normotensive subjects. Biol Exp Hypertens A, Trace Elem Res, Med Sci Monit, 8: Pharmacol Exp Ther, Effect of chronic renal leptin concentrations in normal-weight and obese humans. N Engl J medullary nitric oxide inhibition on blood pressure. Am J Physiol, Med, Region-specific leptin resistance leptin resistance: Diabetes, within the hypothalamus of diet-induced obese mice. Role of nitric oxide in the regulation of nephron stimulation on renal function in the primate. Am J Physiol, Am J Physiol Renal Physiol, Selective resistance correlates of

leptin with hypertension-related phenotypes in African to central neural administration of leptin in agouti obese mice. Role of selective treatment with perindopril, pindolol or felodipinon plasma leptin leptin resistance in diet-induced obesity hypertension. Diabetes, concentration in patients with essential hypertension.

Chapter 4 : - NLM Catalog Result

Role of leptin in blood pressure regulation and arterial hypertension. Beltowski, Jerzy Journal of Hypertension. 24(5), May

Leptin is a hormone-like cytokine or adipokine secreted mainly from adipose tissue. As this resistance builds up, the intake of food increases causing an enhancement in body adiposity and leptin levels. However, some pathways do not build resistance to leptin and continue to exhibit the stimulatory effects, which cause a persistent stimulation of sympathetic nervous system SNS , particularly in the kidneys and skeletal muscles. The increase in SNS activity in the kidney, along with the endothelial dysfunction and oxidative stress, lead to an increase in blood pressure. In this review, an attempt has been made to highlight different aspects of leptin biology, which are relevant to hypertension. Nevertheless, there remains a great deal we do not understand about how leptin works precisely. It has long been established that obesity increases the risk of metabolic syndrome and cardiovascular disease and that this increased risk is due, at least in part, to the increase in blood pressure that tends to follow increased adiposity. However, discovering the cause of hypertension in obesity could revolutionize the way that we treat obesity-related hypertension. Recent studies have implicated leptin in the pathogenesis of hypertension in the obese population due to leptin resistance in the arcuate nucleus and selective activation of a sympathetic nervous response in the kidneys and skeletal muscle. In this review, an attempt has been made to focus primarily on different biological mechanisms that are linked to blood pressure regulating role of leptin. For this purpose, PubMed system has been used largely to search for relevant literature. The discussion of this paper i. Finally, various important issues such as effects on autonomic nervous system, kidney and cardiovascular systems have been discussed in relation to both health and disease conditions. In a physiological state, when energy supply is adequate, leptin is released from adipocytes to alert the hypothalamus, and, in particular, the arcuate nucleus, that enough food has been consumed. Moreover, leptin promotes energy expenditure in the form of thermogenesis and sympathetic nerve activity SNA in the kidneys and adrenal glands. When food supply is scarce, leptin levels fall, triggering an adaptive neuroendocrine response. This response leads to decrease in reproductive hormones, thyroid hormone and insulin-like growth factor, and increase in growth hormone to mobilize energy stores Mantzoros et al. Leptin also plays a role in wound healing, hematopoiesis, osteogenesis, insulin secretion and sensitivity, and glucose homeostasis Figure 1. Pathological effects of leptin in obesity In the obese individual, the increase in adiposity creates an increase in leptin secretion and a state of chronic hyperleptinemia. In this state, the role of leptin becomes pathological. Leptin continues to act on other hypothalamic targets, which continue to stimulate renal and muscular sympathetic nervous system SNS activity Reed et al. The SNS stimulation appears to be selective in its targets, generating functional disruption in the autonomic nervous system ANS. Since the feedback loop between increased leptin levels and satiety has been interrupted, the leptin levels continue to rise, leading to continuous stimulation of sympathetic activity and this imbalance leads to endothelial damage and increased arterial pressure. The mechanism of SNS activation in the state of obesity involves hyperleptinemia, activation of the central nervous system CNS melanocortin and renin-angiotensin-aldosterone systems RAAS , hypoadiponectinemia, hypoghrelinemia, hyperinsulinemia, and baroreflex dysfunction da Silva et al. The primary emphasis of this paper is the impact of the chronic exposure to obesity-induced hyperleptinemia and the cascade of events that ensue. Leptin and melanocortin system While chronic high levels of leptin, which is seen in obesity, have been shown to build increasing resistance to its anorexigenic effects, the stimulation of sympathetic nerve continues to rise as leptin levels rise. To understand how some leptin functions are quelled in chronic hyperleptinemic states while others continue to be stimulated is essential to our understanding of the role of leptin in metabolic dysfunction, hypertension and cardiovascular diseases. However, when MC4R receptors are blocked only sympathetic nerve activity to the kidneys is affected Haynes Interestingly, MC4R deficient mice are hyperphagic, obese, and display signs of

metabolic syndrome, but are not hypertensive, despite high levels of leptin. Likewise, deletion of POMC neuron leptin receptors continue to cause mild obesity, without the hypertensive effects of chronic hyperleptinemia da Silva et al. In contrast, yellow Agouti-overexpressing mice are resistant to the anorexigenic effects of leptin while renal SNA remains intact, causing hypertension. These mice are very similar to the diet-induced obesity DIO mouse model, indicating that leptin resistance in the AgRP neurons of the arcuate nucleus plays a large role in obesity-induced hypertension Haynes A recent study by Purkayastha et al. The study also reported that this form of hypothalamic inflammation-induced hypertension involved the sympathetic upregulation of hemodynamics and POMC neurons that has a crucial role in obesity-related hypertension Purkayastha et al. Leptin and intracellular signaling Though different studies have been able to draw a strong correlation between various neurons of the hypothalamus and their pathophysiological response to hyperleptinemia, the underlying intracellular signaling pathways are not well understood. Selective leptin resistance occurs due to the different biochemical pathways initiated by leptin, and there are a number of negative feedback loop initiators that have been implicated in this complicated process. Studies have shown that even inhibitors of leptin signaling pathways react differently and are preferentially upregulated in different cell types. When leptin binds with its receptor on the cell surface of a hypothalamic neuron, it initiates a conformational change that leads to intracellular activation of JAK2 and phosphorylation of the Src homology2 domain of STAT3. This pathway induces the production of suppressor of cytokine signaling SOCS 3 as a negative feedback mechanism. In high leptin states, these leptin-stimulated pathways are increasingly inhibited by SOCS3 Figure 3. However, when the mice were transgenically modified to overexpress SOCS3 in Ob-Rb neurons no obesity was noted and, in fact, the mice were shown to have a small but significant drop in weight and food intake and in leptin levels, compared to their wild type counterparts. This was an unexpected finding and supports the theory that SOCS3 may influence different Ob-Rb expressing neurons in different ways Reed et al. This was further supported by Pedroso et al. They found that when SOCS3 was deleted at the neuronal level, the result was improved glucose homeostasis and partial prevention of DIO. However, when SOCS3 was inactivated only in Ob-Râ€”expressing cells there was no change to the effects of DIO, but these mice were protected against diet-induced insulin resistance. Though both SHP2 and IRS2 have been implicated in leptin induced intracellular activation, deletion of either of these substances in the entire brain or forebrain, only produce mild hyperphagia and obesity da Silva et al. Protein-tyrosine phosphatase-1B PTP1B has also been shown to dephosphorylate JAK2 in hyperleptinemia and knockout mice have increased leptin sensitivity and reduced body weight Mantzoros et al. Leptin and blood brain barrier A major component of leptin resistance is possibly an impaired transport of leptin across the blood-brain barrier BBB. Investigators have suggested the existence of an active transport system via Ob-Ra Rivest The impaired transport across the BBB could be due to saturation in the transport of leptin and a subsequent decrease in transport activity. This appears to be supported by the decrease in cerebral spinal fluid CSF leptin levels to serum leptin levels in obese individuals. However, it has also been noted that obese individuals still have higher CSF levels of leptin than their lean counterparts Haynes In addition, hypertriglyceridemia has been demonstrated to inhibit the transport of leptin across the BBB, thus attenuating the leptin signal across the BBB and providing a mechanism for peripheral leptin resistance Banks It has also been noted that different brain regions are saturated at different concentrations. When mice models were centrally injected with leptin equivalent to normal limit concentrations for lean humans, the hypothalamus was shown to reveal a preferentially higher concentration than any other brain region. However, when mice were centrally injected with leptin levels mimicking those of obese humans, the hypothalamus showed the lowest leptin concentration of all brain regions. This study implies that different brain regions may have different leptin level thresholds to be activated and may contribute to the clinical finding of selective leptin resistance Mantzoros et al. These actions are simultaneous pressor and depressor effects by inducing activation of SNS causing vasoconstriction and also increase production of nitrous oxide NO by the endothelium, mediator of vasodilation. Studies were performed to delineate the role of leptin on endothelium-dependent vasodilation as

well as endothelium-independent vasodilation Freeman et al. Mice treated with leptin depicted no significant change in endothelium-independent vasodilation in response to sodium nitroprusside. Yet, in response to acetylcholine there was a significant reduction in endothelial-dependent vasodilation in leptin-treated mice. On the other hand, leptin deficient obese mice expressed impaired endothelial relaxation in the presence of acetylcholine that was corrected by exogenous leptin treatment. These experiments have demonstrated leptin as a potent vasodilator and indicated the presence of leptin receptors on endothelial cells Wang et al. Endothelial dysfunction is a result of the oxidative damage that is caused by prolonged state of obesity-induced hyperleptinemic effect of increasing reactive oxygen species ROS. It is of significance to note that short-term exposure of endothelial cells to leptin has been demonstrated to serve as a benefit by stimulating endothelial NO synthase eNOS. However, long-term exposure of the endothelial cells to leptin actually resulted in decrease NO availability. Among free radicals, superoxide and peroxynitrite in particular have been shown to be increased through the stimulation of endothelial cells by excessive leptin Korda et al. When a superoxide scavenger, membrane-permeable piperidine nitroxide tempol, was administered to mice there was no endothelial dysfunction observed under the influence of leptin Wang et al. In DIO mouse models, increased leukocyte-endothelial interactions were seen to correspond with the damage of endothelial cells. The functional vascular impairments are predictive of cardiovascular complications that may occur later. Nitric oxide release The role of NO, in a normal physiological state, consists of far more than vasorelaxation. NO has an inhibitory action on oxidation of low-density lipoprotein LDL , leukocyte migration to the subendothelial space, smooth muscle cell SMC proliferation and migration, platelet adhesion and aggregation. NO reduces the expression of adhesion molecules and increases blood flow to hinder coagulation â€" all function to protect vascular integrity. This mechanism was further examined by the administration of leptin to mice that were pretreated with a NOS inhibitor, resulting in an increased blood pressure Beltowski Essentially, in non-obese individuals, in the presence of eNOS leptin induces NO release to cause vasodilation, whereas independent of eNOS or in the event of its inhibition, leptin causes vasoconstriction and increase in blood pressure. Hence, it is suggestive that vascular leptin-resistance may exist in obese individuals. In one particular study, leptin was administered in a pulsatile manner to avoid inducing leptin resistance, nonetheless assuring that the same obese levels of leptin were infused. After one week of leptin treatment in this manner, diminished ability of the endothelium relaxation was observed Wang et al. Experiments have exhibited impairment of the stimulatory effect of leptin on NO in chronic hyperleptinemia Beltowski Therefore, this impairment of leptin induced NO-mediated vasorelaxation probably contributes to leptin-induced hypertension in obesity. In obese microenvironment there is selective increase in SNS activity to particular organs. Skeletal muscle and kidneys demonstrate elevated SNS activity whereas due to baroreflex inhibitory effect, cardiac sympathetic activity is minimally or not increased. Leptin activates the SNS by local peripheral actions and by the effects on hypothalamus that are centrally mediated. Studies have shown that acutely administered leptin did not affect the blood pressure if it was injected peripherally, whereas central infusion in DIO rats caused resistance to the actions of leptin in peripheral organs such as the kidney Freeman et al. Furthermore, the same rise was observed in non-obese mice that were subjected to modest weight gain da Silva et al. In animals in which SNS was inhibited, leptin was shown to reduce the blood pressure by other factors including NO-mimetic effect on the endothelium Beltowski Again, these studies confirm the normal contrasting function of leptin that involves the balanced activation of vasoconstriction by SNS and vasorelaxation by NO, cancelling out any changes in blood pressure. The only way that the depressor response to leptin can be preserved is by sympathectomy. The factors that contribute to increase SNS activity include blunted baroreflex sensitivity, Angiotensin II release, hyperleptinemia, hypoadiponectemia, hyperinsulinemia, and hypoghrelinemia. Leptin works in synergy by enhancing the presser effect of angiotensin II in acute or chronic treatment. Rats on high sodium diets have chronic vasoconstriction response to angiotensin II, an effect that is eliminated in the event of celiac ganglionectomy. Consequence of the denervation was recovery of the leptin-induced impairment of endothelial-dependent vasodilation in response to acetylcholine; blockage of

leptin-induced supplementation of angiotensin II action to increase systolic blood pressure Wang et al. Leptin and renal function Short-term administration of leptin depicted a natriuretic property of the hormone in rats, increasing excretion of sodium and water, primarily acting at the tubular level. However, in the setting of obesity, leptin has not been shown to increase sodium excretion that might cause an abnormal renal-pressure natriuresis. Impairment of this normal sodium excretion function of leptin in hyperleptinemia participates in causing obesity-related hypertension as a result of sodium retention and a rightward shift in the pressure-natriuresis curve da Silva et al. It may therefore be suggested that the environment of hyperleptinemia may cause renal leptin resistance similar to central resistance to leptin impairing the anorectic effect of leptin. When obese rats were placed on calorie-restricted diets, renal regeneration of NO took place that then participated in the restoration of the natriuretic function of leptin Freeman et al. Potential causes of renal-leptin resistance in obesity-associated hypertension include oxidative stress as a result of excessive degradation of NO, Ob-R downregulation, post-receptor signaling alterations or antinatriuresis resulting from increased activation of the efferent renal SNS. The latter was supported by a study in which kidney nerve supply was surgically removed resulting in the restoration of leptins natriuretic actions.

Chapter 5 : Obesity Hypertension: The Regulatory Role of Leptin - Europe PMC Article - Europe PMC

Ameliorating "renal leptin resistance" or reducing leptin level and/or leptin signaling in states of chronic hyperleptinemia may be a novel strategy for the treatment of arterial hypertension associated with the metabolic syndrome.

Vasc Health Risk Manag. Published online Jun. All rights reserved This article has been cited by other articles in PMC. Abstract Leptin, a peptide discovered more than 10 years ago, decreases food intake and increases sympathetic nerve activity to both thermogenic and nonthermogenic tissue. Leptin was initially believed to be an anti-obesity hormone, owing to its metabolic effects. However, obese individuals, for unknown reasons, become resistant to the satiety and weight-reducing effect of the hormone, but preserve leptin-mediated sympathetic activation to nonthermogenic tissue such as kidney, heart, and adrenal glands. Leptin has been shown to influence nitric oxide production and natriuresis, and along with chronic sympathetic activation, especially to the kidney, it may lead to sodium retention, systemic vasoconstriction, and blood pressure elevation. Consequently, leptin is currently considered to play an important role in the development of hypertension in obesity. Hence, hypertension in obesity has become a topic of extensive ongoing research. Now, several mechanisms have been implicated in the association between obesity and hypertension, including activation of sympathetic nervous system, abnormal renal sodium handling, insulin resistance, and physical compression of the kidney Haynes et al In this respect, sympathetic activation appears to mediate at least part of the obesity-induced hypertension, and leptin, the adipocyte-derived hormone, has recently been postulated as one of the possible causes of this sympathetic activation in obesity. Leptin is a amino acid hormone discovered in that is almost exclusively produced by adipose tissue and possibly secreted by a constitutive mechanism. The effects of this peptide are mediated by receptors Ob-R , most of them located in the hypothalamus, belonging to the class l cytokine receptor family. As of yet, 6 leptin receptor isoforms are known Ahima and Flier Leptin is considered a homeostatic hormone regulating food intake and body weight. Acting on the hypothalamic nuclei, leptin decreases appetite, and increases energy expenditure through sympathetic activation, which consequently decreases adipose tissue mass and body weight. The hormone levels are decreased during fasting and increased after several days of overfeeding as an effort to help regulate energy balance in humans. Due to latter homeostatic control mechanism, leptin is an anti-obesity hormone, based on the hypothetical fact that high leptin levels would prevent the occurrence of obesity. Unfortunately, this is not the case, and so the strong correlation between serum leptin levels and body fat mass found in obese individuals now suggests the existence of an endogenous leptin-resistant mechanism in obesity Considine et al In addition to regulating food intake and adipose tissue mass, leptin has been found to be involved in cardiovascular physiological processes like sympathetic nerve system activation, renal hemodynamics, blood vessel tone, and blood pressure. This review will focus on the leptin-mediated sympathetic activation and its relevance to the mechanism of obesity-related hypertension. Concept of selective leptin resistance As stated above, obesity is associated with high leptin levels, reflecting the increased amount of adipose tissue in obese individuals. As a consequence, it has been postulated that the apparent loss of the anorexic and weight-reducing effects of leptin in obesity, is a result of a leptin-resistance mechanism. Nevertheless, obesity is associated with increased sympathetic nerve activity, and leptin has been proven to participate in autonomic nervous system control, in part, by increasing renal sympathetic nerve activity RSNA. Therefore, it is contradictory that, in the presence of a leptin resistance state, the hormone can contribute to the sympathetic activation seen in obesity. This has led to the novel concept of selective leptin resistance, in which resistance appears to be primarily limited to the metabolic satiety and weight-reducing actions of leptin, sparing the renal sympathetic activation effects. This concept has emerged from observations made first in agouti yellow obese Ay mice Correia et al ; Rahmouni et al , and corroborated recently in a diet-induced obesity model Rahmouni et al In these studies, leptin administered peripherally produced increase in RSNA in both obese and lean mice, but failed to decrease food intake and body weight in the obese mice to a similar degree as it did in their

lean littermates. Interestingly, this same effect was observed when leptin was injected into the lateral ventricle of the brain Rahmouni et al , Here, leptin increased RSNA again, without changing significantly food intake and body weight in Ay and diet-induced obese mice, as compared with their respective lean littermates. These latter studies also served to demonstrate that is unlikely that leptin resistance is due to an impaired leptin transport mechanism across the bloodâ€"brain barrier as intracerebroventricular administration of the hormone also failed to enhance food intake and weight loss. Moreover, the increased RSNA achieved by central leptin administration was not accompanied by changes in plasma leptin levels, suggesting that leptin-induced RSNA was centrally-mediated. In agreement with these observations, Munzberg et al recently described that leptin resistance is not global within the hypothalamus, and found that the arcuate nuclei, which contains leptin-mediated anorexigenic neurons, becomes resistant to leptin in very early stages of diet-induced obesity in mice. On the contrary, other hypothalamic and extrahypothalamic sites appear to continue relatively sensitive to the actions of leptin, including the ventromedial hypothalamic nuclei, which has been previously shown to mediate leptin-induced sympathetic nerve activation Satoh et al This hypothesis, however, must be proved in human studies as well, and if true, it would help explain how leptin could contribute to sympathetic activation and hypertension despite the fact that there is resistance to the satiety and weight-reducing effects of leptin in obesity. Renal effects of leptin: The renal effect of leptin also depends on the exposure time to the hormone. As it has been observed, acutely administered leptin usually does not increase blood pressure in animal or human studies, but when given for longer periods of time, leptin does elevate blood pressure in animal models. Acute effects Traditionally, obesity-induced renal sympathetic activation has been thought to contribute to the development of hypertension by enhancing sodium retention, since renal denervation attenuates the antinatriuretic and hypertensive effect of obesity in dogs Kassab et al Although systemic administration of leptin stimulates sympathetic nerve activity to the kidney Haynes, Morgan, et al , if infused for short period of time, leptin produces increased sodium excretion and urine output with no changes in blood pressure in lean animals Jackson and Li ; Villarreal et al ; Beltowski, Wojcicka, Gorny, et al ; Beltowski, Jochem, et al The increased natriuresis and fractional sodium excretion are not accompanied by substantial changes in glomerular filtration rate or the reninâ€"aldosterone axis suggesting a decreased sodium tubular transport. New evidence suggests that leptin stimulates systemic NO release which opposes the pressor and antinatriuretic effect of leptin-induced sympathetic activation Beltowski, Wojcicka, Borkowska, et al ; Beltowski, Jochem, et al In this regard, Vecchione et al demonstrated that leptin stimulates NO production in endothelial cells and blood vessels. In other studies, leptin evoked a hypotensive effect when the sympathetic nervous system output was blocked pharmacologically, implying a likely leptin-mediated vasorelaxant effect Fruhbeck ; Lembo et al Likewise, Villarreal et al found that chronic inhibition of NO synthesis impairs the acute leptin-mediated natriuretic effect in normotensive lean rats. The kidney has been shown to express high amounts of leptin receptors Serradeil-Le Gal et al , yet it is not clear whether leptin evokes a direct effect on leptin receptors or indirectly via induction of NO release in renal tubules. Interestingly, the short-term leptin-induced natriuretic effect seen in lean animals was attenuated in obese rats and was even blunted in spontaneously hypertensive rats SHR Villarreal et al ; Beltowski, Wojcicka, Gorny, et al In agreement with this statement, Villarreal et al found that SHR after renal denervation recovered the sodium excretory capacity in response to acute leptin administration. Recent data indicate that chronic hyperleptinemia decreases natriuresis and urinary excretion of NO metabolites NOx Beltowski, Jamroz-Wisniewska, et al In humans, a negative correlation between leptin and NOx was observed recently in obese hypertensive individuals Golan et al Apparently, long-term hyperleptinemic states like obesity increase the level of systemic and intrarenal oxidative stress, leading to NO deficiency Beltowski, Wojcicka, et al Supporting these observations, Bickel et al reported an increased number of different sodium tubular transporters in the kidney of obese rats. These animals exhibited a decreased natriuretic effect after a saline load when compared with their lean age mates. Clinical relevance Chronic hyperleptinemia, as mentioned, augments the blood pressure by means of different mechanisms in animal models. In humans, there have been several studies attempting to link leptin to

hypertension Figure 1. Serum leptin levels are elevated in obesity due to increase amount of adipose tissue which is the main source of the hormone and possibly secondary to some degree of central resistance to its action. A number of studies have found leptin to be positively correlated with systolic and diastolic blood pressure in both obese Kunz et al ; Golan et al ; Itoh et al ; Al-Hazimi and Syiamic ; Canatan et al a ; Schutte et al and non-obese individuals Uckaya et al ; Adamczak et al ; Takizawa et al ; Barba et al ; Canatan et al b. Al-Hazimi and Syiamic , for example, found that serum leptin and angiotensin II levels were strong predictors of elevated blood pressure in obese women. Likewise, other investigators Kunz et al ; Golan et al ; Canatan et al b reported higher leptin levels in obese hypertensives compared with obese normotensive individuals, even after controlling for confounders such as age and body mass index BMI. In another study leptin correlated stronger with systolic and diastolic blood pressure than did with BMI or waist circumference in untreated male adults Barba et al Moreover, one study found that after a 3-month weight reduction program, leptin continued to correlate positively with mean arterial blood pressure in the hypertensive, but not in the normotensive obese group Itoh et al Interestingly, leptin has been found to be elevated in several hypertensive states of pregnancy as well Anato et al ; Vitoratos et al For instance, Vitoratos et al reported increased leptin levels in pre-eclamptics compared with normotensive pregnant women of the same gestational age. Of note is also the observation that a positive correlation between leptin and platelet count levels exist in pre-eclamptic women Anato et al

Chapter 6 : The Role of Topical and Oral Melatonin in Management of Melasma Patients

To understand how some leptin functions are quelled in chronic hyperleptinemic states while others continue to be stimulated is essential to our understanding of the role of leptin in metabolic dysfunction, hypertension and cardiovascular diseases.

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Consequently, leptin is currently considered to play an important role in the development of hypertension in obesity. Keywords: leptin, renal sympathetic nerve activity, blood pressure, obesity, selective leptin resistance, nitric oxide, natriuresis.

Chapter 8 : Role of leptin in blood pressure regulation and arterial hypertension

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